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**Alendronate and Hormone Replacement Therapy in the Prevention of
Osteoporotic Fracture: A Pharmacoeconomic Analysis Employing a
Net-Benefit Regression Method of Cost-Effectiveness**

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Osteoporotic Fracture: A Pharmacoeconomic Analysis Employing a
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by

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Alendronate and Hormone Replacement Therapy in the Prevention of Osteoporotic Fracture: A Pharmacoeconomic Analysis Employing a Net-Benefit Regression Method of Cost-Effectiveness

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Osteoporosis is a common chronic condition which poses a substantial clinical, economic, and health-related quality-of-life (HRQOL) burden to the individual, the U.S. health care system, and society in general. The overall objective of this study was to evaluate the economic, clinical and humanistic outcomes of current osteoporosis interventions employed in the prevention of osteoporotic fractures in the Department of Defense (DoD) population. The overall objective encompassed four primary objectives: to assess the epidemiology of osteoporotic fracture in women \geq age 50; to determine the effectiveness of current osteoporosis interventions; to identify significant risk factors and other covariates in the prediction of osteoporotic fracture; and to determine the cost-effectiveness of current osteoporosis interventions. A three-year sample-based retrospective cohort study was conducted using DoD health care and prescription claims from fiscal years 2000 to 2003. Using an intent-to-treat study design, a total of 49,851 women \geq age 50 were followed for osteoporotic fracture. The effectiveness of the

interventions was determined by performing a series of both logistic and direct Cox proportional hazard regressions. The net-benefit regression method of cost-effectiveness was employed to determine the cost-effectiveness of the treatment interventions and to determine the importance of covariates on the marginal cost-effectiveness of an intervention, while statistically controlling for the presence of risk factors and other covariates. The epidemiologic study results showed that the three-year cumulative incidence of an osteoporotic fracture was 2.5 % for the cohort (0.4% in patients without a diagnosis of osteoporosis; 6.1% in patients with a diagnosis of osteoporosis). The intervention effectiveness results obtained from the logistic regression model and the direct Cox proportional-hazards model were consistent and suggested that women treated with the combination of alendronate and HRT are at a lower risk for any fracture, hip fracture, and vertebral fracture when compared to no treatment. In contrast, treatment with alendronate or HRT alone was not found to provide a statistically significant decreased risk of any fracture, hip fracture, vertebral fracture, or wrist fracture when compared to no treatment. The results of this study revealed that the risk of osteoporotic fracture increased: 4-fold with a prior fracture, 4% with each year over 50, and between 38 and 55% with oral corticosteroid use > 1-year (in a three-year period). The findings also suggest that statin use was associated with a decreased risk of osteoporotic fracture. The results from the net-benefit regression method of CEA showed that the current use of DoD's osteoporosis treatment interventions is not cost-effective in the short-term when compared to no treatment. However, this study provided evidence that the current treatment interventions become more cost-effective when targeted at high risk populations, such as patients with a prior osteoporotic fracture or patients \geq age 65. The results of this study were potentially influenced by the presence of selection bias.

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Chapter 1

Literature Review

INTRODUCTION

Osteoporosis is a common chronic condition with a substantial clinical, economic, and health-related quality-of-life (HRQOL) burden to the individual, the U.S. health care system, and society in general. Osteoporosis and osteopenia (low bone mass) pose a major public health threat to an estimated 44 million Americans ≥ 50 years of age. In the U.S., an estimated 10 million (8 million women, 2 million men) individuals already have osteoporosis and 34 million have osteopenia.¹ Osteoporosis is a systemic disease characterized by low bone mass and structural deterioration of the bone tissue, which leads to bone fragility and increased susceptibility to fractures.² Approximately, 1.5 million osteoporotic fractures occur annually, of which there are approximately 300,000 hip fractures, 700,000 vertebral fractures, 250,000 wrist fractures, and 300,000 fractures at other sites.¹ In 1995, osteoporotic fractures were responsible for 3.4 million office and emergency room visits, 180,000 nursing home admissions, and over 400,000 hospitalizations. In the same year, the direct economic cost was estimated to be \$14 billion.³ A more recent estimate places the direct annual medical costs associated with osteoporotic fractures to the U.S. healthcare system at \$17 billion (2001 dollars).³ The economic burden of osteoporosis is projected to potentially triple by the year 2040, given the aging U.S. population.²

Osteoporosis is a chronic asymptomatic disease for many women, with some not even aware of their low bone mineral density (BMD). However, as the disease

progresses and the severity of osteoporosis increases, patients become more likely to experience the physiologic impact of osteoporosis: skeletal fractures, height loss, and kyphosis resulting from vertebral fractures. Although mortality has been associated with hip and more recently vertebral fracture⁴, the primary impact of osteoporotic fractures is not on the individual's quantity of life but instead on the individual's health-related quality-of-life (HRQOL). The impact of osteoporosis affects not only the individual's physical but also the psychological and social dimensions of HRQOL. It is most often the physical manifestations of osteoporosis (i.e., diminished functional status and pain) that subsequently lead to the deterioration of the psychological (i.e., anxiety, depression, and low self-esteem) and the social (social support and roles function) dimensions of HRQOL. However, some studies indicate that even the diagnosis of osteoporosis has led to an altered self-perception and illness behavior.⁵

The remainder of Chapter 1 is divided into eight sections. The next section provides the generally recognized definition, diagnosis criteria, and treatment threshold for osteoporosis. Also included in this section is a discussion of the epidemiology of osteoporosis and osteoporotic fractures. Sections II and III provide a comprehensive literature review of the clinical trial evidence supporting the efficacy, safety, and tolerability (section II) and an economic assessment (section III) of the Department of Defense's formulary agents for the prevention of osteoporotic fractures (alendronate, hormone replacement therapy (HRT), and the combination of alendronate and HRT). The following section provides an overview of the methodology literature pertinent to the proposed study. Section V discusses the literature to date regarding the association

between statins and fracture and provides justification for the inclusion of statins in any economic assessment of treatment interventions for osteoporotic fracture prevention due to statins potential to act as confounder. Section VI provides a brief overview of the use of retrospective databases in outcomes research. Finally, sections VII and VIII provide the rationale and objectives of the study and the list of null hypotheses, respectively.

OSTEOPOROSIS & OSTEOPOROTIC FRACTURE

Definition

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.⁶

Diagnosis of Osteoporosis

Since as much as 80% of bone strength is dependent upon bone mineral density (BMD),^{7,8} four diagnostic categories have been proposed by the World Health Organization (WHO) and modified by the International Osteoporosis Foundation based on assessment of BMD by dual energy X-ray absorptiometry (DXA) for Caucasian women.⁹⁻¹¹

- Normal: hip BMD \geq 1 SD below the young adult reference mean (T score \geq -1)
- Osteopenia: hip BMD \leq 1 SD below the young adult reference mean, but $>$ than 2.5 SD below the young adult reference mean (T score $<$ -1 and $>$ -2.5)
- Osteoporosis: hip BMD \leq 2.5 SD or more below the young adult reference mean (T score \leq -2.5)

- Established osteoporosis: hip BMD \leq 2.5 SD or more below the young adult reference mean (T score \leq -2.5) in the presence of one or more fragility fractures.

Dual energy X-ray absorptiometry (DXA)¹¹ and BMD measurement at the hip¹² are the gold standards for measurement of BMD in the diagnosis of osteoporosis. The WHO and International Osteoporosis Foundation recommend the use of the National Health and Nutrition Examination Survey (NHANES III) reference database in women aged 20-29 years as the BMD reference range.¹¹

Treatment Threshold

The National Osteoporosis Foundation (NOF) recommends treatment for all postmenopausal women who present with vertebral or hip fracture, women who have BMD T-scores below -2 and women who have T-scores below -1.5 as well as additional risk factors, especially prior fracture.¹³

Epidemiology of Osteoporosis and Osteoporotic Fractures

Osteoporosis primarily affects postmenopausal women. Using criteria established by the WHO, approximately 13% to 18% of U.S. women \geq 50 years of age have osteoporosis and another 37% to 50% have osteopenia.¹⁴ The NOF currently estimates that approximately eight million U.S. women have osteoporosis and an additional 22 million women have osteopenia.¹⁵ As the U.S. population ages, the prevalence of osteoporosis and osteopenia will increase. The NOF estimates that by 2020, 14 million men and women will have osteoporosis and another 48 million will have osteopenia.² Osteoporotic fractures, along with their associated morbidity and mortality, provide the clinical significance of osteoporosis.

The NOF estimates that osteoporotic fractures will occur in one in two women and one in eight men after age 50.¹ North American women ≥ 50 years of age have an estimated life-time risk of 18% for hip fracture, 16% for clinically diagnosed vertebral fracture, and 16% for Colles' (wrist) fracture.^{16, 17} The estimated annual incidence of osteoporotic fractures in the U.S. is >1.5 million, of which there will be approximately 700,000 vertebral fractures, 300,000 hip fractures, 250,000 wrist fractures, and 300,000 fractures at other sites.¹ The one-in-six lifetime risk of hip fracture is greater than the reported one-in-nine risk of developing breast cancer.^{17, 18} Of the one million hip and spine fractures, 90% will be due to the underlying condition of osteoporosis.¹⁹ The actual prevalence of vertebral fractures in U.S. women could vary by up to three-fold, dependent on the criteria used to define vertebral fracture.²⁰⁻²² Moreover, only about one-third of all vertebral deformities noted on radiographs come to medical attention with less than 10% necessitating hospital admission.²³

Risk Factors for Osteoporosis and Osteoporotic Fracture

The pathogenesis of osteoporotic fracture is multi-factorial with many risk factors having been identified. Table 1.1 below provides a list of clinically important risk factors. Low BMD and past or current history of fracture are the strongest predictors of osteoporotic fractures among elderly women.^{24, 25}

Bone Mineral Density (BMD)

Given that BMD explains 60% to 85% of bone strength variance,²⁶ research has demonstrated that the ability to predict hip fracture from measurement of BMD is at least as good as the measurement of blood pressure in predicting stroke, and considerably

better than the measurement of serum cholesterol in predicting coronary artery disease.^{10,27} Research has shown that: each standard deviation (SD) decrease in lumbar spine BMD is associated with about a 2-fold increase in spine fracture risk;¹² a 1 SD decrease in femoral neck BMD²⁸ is associated with a 2- to 3-fold increase in hip fracture risk (among women ≥ 65 years); and a 2.5 SD decrease in trochanteric hip BMD is associated with a 6-fold increase in hip fracture risk (among women ≥ 70 years).²⁵

Table 1.1 Risk factors for osteoporosis and osteoporotic fracture^{7, 13, 24, 29-31}

<p>Demographic Factors</p> <ul style="list-style-type: none"> • Advanced Age* • White or Asian ethnicity • Female Sex <p>Skeletal Factors</p> <ul style="list-style-type: none"> • Low BMD • High bone turnover with excessive bone resorption* • Prevalent vertebral deformities/fractures • Hip axis length • Presence of an existing fracture • History of maternal fracture • Personal or family history of osteoporosis and/or osteoporotic fracture* <p>Behavioral Factors</p> <ul style="list-style-type: none"> • Smoking* or excessive alcohol intake • Low level of physical activity • Low calcium and vitamin D intake <p>Clinical/Medical Factors</p> <ul style="list-style-type: none"> • History of recurrent falls • Estrogen deficiency (women) - primary or secondary amenorrhea, premature menopause • Hypogonadism (men) • Long-term immobilization • Low body weight and body mass index* • Impaired neuromuscular function* (slow gait, decreased quadriceps strength) [inability to rise from a chair, reduced grip strength] • Impaired vision* (decreased acuity or depth perception) • Impaired cognition • Environmental hazards (e.g., throw rugs, slippery floors) • Disease (e.g., congestive heart failure, renal failure, cystic fibrosis, chronic pulmonary disease, hepatic disease, hyperthyroidism, malabsorptive disorders, myeloma, local neoplasm, parathyroid disease, • Solid organ transplantation • Certain medications: anticonvulsants, antipsychotics, long-acting benzodiazepines, corticosteroids*, sedatives, and tricyclic antidepressants

* Denotes risk factors that increase fracture risk over and above that provided by BMD

Personal History of Fracture

Apart from BMD, a personal history of fracture is one of the strongest clinical predictors of subsequent fractures.³² It has been shown that a past history of

postmenopausal fracture confers a 4-fold increase in the risk of hip fracture relative to a negative fracture history.²⁵ A past history and/or current presence of a symptomatic or asymptomatic vertebral fracture(s) and/or deformities is a strong predictor of the subsequent risk osteoporotic fractures.

- Vertebral fracture increases the risk of additional fractures by at least 4-fold (independent of BMD).³³
- One in five women with an existing vertebral fracture will experience another vertebral fracture within the following year, with risk increasing as numbers of baseline vertebral fractures increases.²⁴
- Baseline vertebral deformities increase the risk of hip fracture 3-fold and non-vertebral fractures 2-fold.³⁴
- Vertebral deformity increases the risk of sustaining another vertebral fracture more than 12-fold during a 10-year period.³⁵
- Vertebral fracture increases the risk of subsequent hip fracture 2.3-fold and Colles' fracture (wrist) 1.6-fold during a 10 year period.³⁵
- The presence of two or more prevalent vertebral fractures increases fracture risk for any specific BMD 12-fold.³⁶

The most devastating osteoporotic fracture is fracture of the hip. The risk of hip fracture is increased after previous fracture at the hip > 2.0-fold, the spine > 2.0-fold, and the forearm and proximal humerus 2.0-fold. Risk of vertebral fracture is similarly increased after a previous fracture at the hip 2.5-fold, the spine 4.4-fold, the forearm 1.7-fold, or the proximal humerus 1.9-fold.³²

Age

NHANES III data captured in the 1990s provided evidence that the prevalence of osteoporosis among Caucasian women increased with age. The proportion of women with osteoporosis increased sharply from less than 1% of women aged ≤ 30 , to 4% of women aged 50-59, to 20 % of women aged 60-69, to 34% of women aged 70-79, and to 52% of women aged 80-89.³⁷

The risk of osteoporotic fractures also increases with age. The lifetime probabilities and 5-year probabilities of various types of fractures at various ages for average-risk Caucasian women have been calculated by the NOF based on the Study of Osteoporotic Fractures (SOF)³⁸ (Table 1.2). The NOF calculated the probabilities based on two competing factors: 1) the probability of having a fracture at any age, which increases with age; and 2) the probability of reaching a given age, which decreases with age.

Table 1.2 The lifetime and 5-year probabilities of various types of fractures at various ages for average-risk Caucasian women²

Fracture Type	Current Age, Years								
	50	55	60	65	70	75	80	85	90
Probability during remainder of life									
Hip	0.1429	0.1413	0.1394	0.1380	0.1360	0.1332	0.1228	0.1016	0.0694
Wrist	0.1438	0.1314	0.1146	0.0926	0.0762	0.0550	0.0420	0.0311	0.0191
Spine	0.1496	0.1467	0.1420	0.1347	0.1251	0.111	0.0916	0.0660	0.0397
Other	0.3123	0.2988	0.2794	0.2590	0.2217	0.1911	0.1564	0.0794	0.0289
Probability in subsequent five-years									
Hip	0.0023	0.0044	0.0055	0.0101	0.0158	0.330	0.0525	0.0719	0.0694
Wrist	0.0158	0.0219	0.0281	0.0232	0.0284	0.0211	0.0202	0.0225	0.0191
Spine	0.0057	0.0098	0.0148	0.0208	0.0291	0.0389	0.0469	0.0489	0.0397
Other	0.0691	0.0882	0.0955	0.1183	0.1089	0.1098	0.1349	0.0765	0.0289

Hip fracture incidence rates increase exponentially with age in postmenopausal women.³⁹ The increased fracture risk can be partly attributed to the age-related decrease in BMD at the proximal femur,¹⁴ but can also be attributed to an age-related increase in falls,⁴⁰ which are responsible for at least 90% of hip fractures.⁴¹ The risk of falls is 2-fold higher in women than men, and this risk increases 2-fold between 60 and 80 years of age.²⁹ In general, for every 10-year increase in age, there is a 70% increase in the risk of a fall.⁴²

Race/ethnicity

Race/ethnicity is an indirect risk factor for osteoporotic fracture due to its association with the prevalence of osteoporosis and osteopenia. Established diagnostic and therapeutic guidelines are based on the BMD of Caucasian women, however women of other racial and ethnic backgrounds are also at risk. According to the same NHANES III data set, 19% of non-Hispanic white women, 17% of Mexican American women, and 11% of non-Hispanic black women aged 50 years or older have osteoporosis.³⁷ Asian American⁴³⁻⁴⁶ and Native American^{47, 48} women have been reported to have BMDs even lower than Caucasian women.

Gender

Women are at higher risk of osteoporotic fractures than men. Similar to age, the increased osteoporotic fracture risk of women compared to men is due to a gender-related decrease in BMD and gender-related increase in falls. Due primarily to these reasons, the incidence of hip fracture in women is about twice that seen in men at any age in the U.S., with more than three-quarters of all hip fractures occurring in women. The lifetime risk

of hip fracture from age 50 for Caucasian women is 17% compared to 6% for Caucasian men and the lifetime risk of a clinically diagnosed vertebral fracture is about 16% in Caucasian women compared to 5% in Caucasian men in the U.S..¹⁸

Corticosteroid Use

Corticosteroid therapy is the most common cause of drug-related osteoporosis, with an estimated 30-50% of patients receiving chronic corticosteroid therapy experiencing fractures.⁴⁹ Corticosteroids increase bone loss, reduce new bone formation, and accelerate osteocyte death, all of which weaken bone. Bone loss is believed to be most rapid in the first few months of treatment and affects both axial and appendicular skeleton, but is most pronounced at the spine. Bone loss is observed even with the use of low doses of corticosteroids, but is most rapid and extensive at doses $\geq 5\text{mg/day}$ of prednisone or its equivalent.⁵⁰⁻⁵³

Other Established Risk Factors for Fracture

The significance of some risk factors is age dependent. Risk factors for falling (impaired neuromuscular function, vision, and cognition, environmental hazards, certain medications, and disease states) are stronger predictors of fracture among the elderly than the young. Hypogonadism is an important risk factor in both males and females. Smoking, alcohol, and poor calcium nutrition have been characterized as weak risks; however, smoking has been found to be a statistically significant risk factor independent of BMD. Complete immobilization leads to rapid bone loss at the affected sites and is an important risk factor; however, there is less evidence to suggest that low levels physical activity increases the risk of osteoporotic fracture. A low body-mass index is an

important risk factor for osteoporotic fracture, given its association with bone size. Finally, a maternal history of hip fracture is an independent risk factor for fracture. For any specific BMD, a maternal history of hip fracture is associated with an approximate 2-fold increased risk of hip fracture.⁵⁴

Morbidity

Although mortality has been associated with hip and vertebral fracture, the primary impact of osteoporotic fractures is the reported reduction of the individual's health-related quality-of-life (HRQOL)^{30, 55} and related functional impairments. It is most often the physical manifestations of osteoporosis resulting from hip or multiple vertebral fractures, diminished functional status and pain, that subsequently lead to the deterioration of the psychological (anxiety, depression, and low self-esteem) and the social (social support and roles function) dimensions of HRQOL. Several studies have examined the impact of hip and vertebral osteoporotic fractures on psychosocial outcomes. Mossey et al.⁵⁶ examined depression in 200 women recovering from hip fractures and concluded that women experiencing high levels of depression after hip fracture surgery were more likely to experience poorer recovery of function. A study conducted by Cook et al.⁵⁷ examined the anxiety, fear, and other emotional reactions in 100 women with osteoporotic vertebral fractures. In this study, the investigators found a high proportion of women with osteoporotic vertebral fractures reported experiencing a fear of falling (82%), fear of new fractures (74%), frustration (66%), anger (53%), and feeling overwhelmed (49%). Paier⁵⁸ conducted a qualitative study in women with

symptomatic vertebral fractures and found that the women experienced a loss of self-esteem, isolation, vulnerability, and embarrassment related to physical appearance.

A further concern is the functional impairment associated with osteoporotic fractures. In general, after allowing for expected functional impairment in old people, fractures of the hip, spine, and distal forearm cause approximately 7% of women to become dependent upon others to help them accomplish the basic activities of daily living and precipitate nursing home care in a further 8%.⁵⁹ As expected, hip fractures contribute the most to this burden.¹⁸ Post hip fracture, the most important long-term impairment is the ability to walk. Approximately 20% of patients who experience a hip fracture are non-ambulatory to begin with, but of those who are ambulatory prior to a fracture, half cannot walk independently afterwards.⁶⁰ The discharge status post hip fracture is age dependent and the likelihood of discharge to a nursing home increases with age. Approximately 1 in 6 patients age 50 to 55 are discharged from the hospital to the nursing home compared to more than half of those older than 90 years.⁶¹ A critical assessment point is one-year post hip fracture. At one-year post hip fracture, only 40% of surviving patients regain their previous level of mobility, and only 25% regain their former functional status.⁶² Of those who lived independently before hip fracture, 50% remain in long-term care or need help with the activities of daily living the year after the event,⁶³ and one-third of patients are admitted to nursing homes.³⁰ Ultimately, up to one-third of individuals who have a hip fracture can become totally dependent.^{64, 65} When elderly women were surveyed, 80% preferred death over admission to a nursing home after a hip fracture.⁶⁶

The morbidity associated with single compression vertebral fractures is primarily limited to acute symptoms and acute pain, which typically resolve over weeks or months.⁶⁷ However, vertebral fractures are often multiple and consequently produce cumulative physical effects, such as dorsal kyphosis (dowager's hump), height loss, chronic pain, loss of pulmonary capacity, impaired gait and balance, digestive problems, and psychological effects such as low self esteem, body image, and mood.^{55, 68-72}

Morbidity is also associated with wrist fractures. Women who sustain wrist fractures often experience long-term sequelae, which includes pain, deformity, and functional impairment.⁷³ At a three-year follow-up post wrist fracture, approximately 75% of patients reported regaining almost full function and 25% of patients reported a variable loss of wrist strength.⁵⁵

Mortality

The mortality associated with hip fractures is the most serious. Approximately 10-20% more women die than expected for age within the first year. This risk is greatest immediately after the fracture and decreases over time.⁷⁴ A few of these deaths can be attributed directly to the hip fracture, but most are attributed to the chronic illnesses that led to both fracture and patient's ultimate demise.^{75, 76} It has been estimated that in the U.S., hip fractures result in 31,000 excess deaths within 6 months of the event.⁷⁷ Vertebral fractures have a raised mortality rate that extends well beyond the first year after the fracture.⁷⁷ The 5-year survival rate is reduced by 16% in women with vertebral fractures.⁵⁵

CLINICAL TRIAL EVIDENCE OF EFFICACY, SAFETY AND TOLERABILITY

A systematic review of the literature was undertaken to compare the efficacy, safety, and tolerability of alendronate, hormone replacement therapy (HRT), and the combination of alendronate and hormone replacement therapy (AHRT) in the prevention of osteoporotic fractures in patients with osteopenia, osteoporosis, or established osteoporosis. The criteria for trials to be included in the review consisted of: 1) randomized placebo-controlled trials (RCTs) of at least one-year's duration (calcium and/or vitamin D controlled trials were accepted as placebo controlled); 2) participants had a diagnosis of osteopenia, osteoporosis, or established osteoporosis; 3) reported vertebral and/or non-vertebral fractures; and 4) were published in English. The results included in this review will focus on fracture outcomes, safety, and tolerability only, thereby excluding commonly reported results pertaining to percent change in bone mineral density (BMD) from baseline, biochemical indices of bone turnover, and percent change in height from baseline. The following literature review will discuss findings from RCTs in the following order - alendronate, HRT, and AHRT.

Alendronate

In all, eight trials^{42, 78-84} were identified that met the inclusion criteria, two^{42, 82} of which were different arms of the Fracture Intervention Trial, the first “mega-trial” of an antiosteoporosis agent. All of the trials were similar in that each recruited primarily Caucasian postmenopausal women with primary osteoporosis or osteopenia and each trial provided participants elemental calcium and/or vitamin D in comparable doses. The studies differed in study duration, sample size, prevalence of previous fractures, mean

age, doses of alendronate, and measurement of vertebral and non-vertebral fractures. The duration of trials ranged from one-year^{80, 83, 84} to 4.2 years.⁸² The sample size of the trials ranged from 188⁷⁸ to 4,432⁸² participants. Several of the trials^{78, 80, 82} excluded participants with a previous history of osteoporotic fractures, one trial⁴² had previous osteoporotic fractures as an inclusion criterion, and another did not measure the risk factor.⁸⁴ The mean age of participants ranged from 59⁷⁹ to 70.8⁴² years of age. The study doses of alendronate ranged from 1mg⁸¹ to 40mg.⁷⁸ Vertebral fractures were reported as a primary outcome in one trial,⁴² and as a secondary outcome in 3 trials.^{78, 80, 81} One study reported clinical (symptomatic) vertebral fractures as a primary outcome and morphometrically diagnosed vertebral fractures as a secondary outcome.⁸² One study reported non-vertebral fractures as a primary outcome⁴² and four trials reported such fractures as secondary outcomes.^{42, 78, 80, 81, 84} In two studies,^{79, 83} clinical fractures were only noted as part of the safety monitoring, of which one study⁷⁹ reported only aggregated figures of vertebral and non-vertebral fractures.

The Fracture Intervention Trial (FIT)^{42, 82} is considered to be the hallmark RCT of alendronate. It was the first mega-trial of an antiosteoporosis agent, which by definition of a mega-trial had the population size and trial duration to provide sufficient statistical power to examine fracture outcomes and their consequences. The FIT enrolled 6,459 postmenopausal women with a hip BMD T-score < -1.6 (2,027 women with prior vertebral fractures⁴²; 4,432 without prior vertebral fractures⁸²). In the FIT (in women with prior vertebral fracture), alendronate reduced the incidence of morphometrically diagnosed vertebral fractures by 47% (RR (relative risk), 0.53; 95% CI, 0.41 to 0.68),

clinical vertebral fractures by 55% (RH (relative hazard), 0.45; 95% CI, 0.27 to 0.72), and all clinical fractures by 28% (RH, 0.72; 95% CI, 0.58 to 0.90) compared to placebo. In the FIT (in women without prior vertebral fractures), alendronate reduced the incidence of morphometrically diagnosed fractures by 44% (RR, 0.56; 95% CI, 0.39 to 0.80), and significantly reduced the incidence of clinical fractures in women with an initial T-score of -2.5 or less (RH, 0.64; 95% CI, 0.50 to 0.82). In the three trials⁷⁸⁻⁸⁰ prior to the FIT, only one trial⁸⁰ demonstrated a reduced incidence in vertebral fractures (RR, 0.52; 95% CI, 0.28 to 0.95) and a trend towards reduction in incidence of fractures at non-vertebral sites (estimated risk 0.79; 95% CI, 0.52 to 1.22). In the three trials^{81, 83, 84} post FIT, two trials^{81, 84} demonstrated a significantly reduced incidence in non-vertebral fractures (RR, 0.53; 95% CI, 0.30 to 0.90;⁸⁴ RR not reported⁸¹).

Kanis et al.⁸⁵ performed a meta-analysis on the clinical trials of alendronate that morphometrically defined a vertebral fracture as a 20% reduction in vertebral height^{42, 80-82} to assess efficacy of alendronate (Table 1.3).

Table 1.3 Efficacy of alendronate: relative risk of fracture⁸⁵

SITE OF FRACTURE	RR (95% CI)
All patients	
• Vertebral	0.544 (0.448 to 0.659)
• Hip	0.611 (0.392 to 0.951)
• Wrist	0.866 (0.672 to 1.115)
• Other	0.862 (0.740 to 1.003)
• All non-vertebral	0.825 (0.736 to 0.926)
Patients with prior fracture	
• Vertebral	0.529 (0.408 to 0.687)
• Hip	0.497 (0.244 to 1.013)
• Wrist	0.528 (0.317 to 0.879)
• Other	0.993 (0.763 to 1.293)
• All non-vertebral	0.811 (0.648 to 1.013)
Patients without prior fracture	
• Vertebral	0.558 (0.387 to 0.805)
• Hip	0.795 (0.438 to 1.443)
• Wrist	1.188 (0.869 to 1.624)
• Other	0.803 (0.662 to 0.967)
• All non-vertebral	0.889 (0.761 to 1.039)

In general, the relative risk reduction of alendronate for vertebral fractures was greater than that for non-vertebral fractures. Significant relative risk reductions were found for vertebral, wrist, and hip fractures, whereas the effects at other sites were not statistically significant. Alendronate had higher relative risk reductions for vertebral (morphometrically or clinically diagnosed) and non-vertebral fractures in patients with a previous vertebral fracture⁴² and in patients with osteoporosis (BMD \geq 2.5 SD below the mean).⁸²

Alendronate was well tolerated in the trials. The most frequent adverse event experienced by participants taking alendronate was upper gastrointestinal (GI) events. However, there was not a statistically significant difference in the rate of adverse events

between alendronate and placebo, including upper gastrointestinal events. It should be noted that the trials excluded participants with a history of gastrointestinal disease. Brief reviews of the clinical trials are provided below.

Chestnut et al.⁷⁸ conducted a two-year, multi-center, double-blind, placebo-controlled RCT to examine a potential “dose-response” effect of alendronate on BMD in postmenopausal women with osteoporosis. A total of 188 postmenopausal (98% Caucasian) women, between 42-75 years of age, with lumbar spine BMD > 2 SD below the mean for young premenopausal women, were assigned by a randomized block allocation schedule to one of six treatment groups: placebo or 5 or 10mg alendronate for 2 years; alendronate 20 or 40mg for one year followed by placebo for one year; or alendronate 40mg for 3 months followed by 2.5mg for 21 months. Evidence of previous spine or hip fracture attributable to osteoporosis was an exclusion criterion. All participants received elemental calcium 500mg/day. The primary outcome measure was BMD of the lumbar spine, proximal femur, forearm, and total body. Secondary outcome measures included the effect on calcium metabolism, biochemical indices of bone turnover, safety and tolerability, vertebral fractures, and non-vertebral fractures. No new vertebral fractures were identified during the study. There were 13 non-vertebral fractures in 12 patients, which were evenly distributed across all treatment groups. Alendronate therapy was well tolerated overall; upper GI intolerance was the most common complaint, which was primarily experienced with the 40mg dose (seven of the nine who withdrew from study medication were taking the 40mg dosage).

Adami et al.⁷⁹ conducted a two-year, double-blind, placebo-controlled RCT, with open-label calcitonin arm to examine the effect of alendronate on bone mass in postmenopausal women affected by osteoporosis. A total of 286 postmenopausal women (Caucasian), between 48-76 years of age, with lumbar spine BMD > 2 SD below the mean for young premenopausal women were randomized to one of four treatment groups: placebo; alendronate 10 or 20mg/day; or intranasal salmon calcitonin 100IU/day. Evidence of previous vertebral fractures was not an entry criterion (only 5% of subjects had prevalent fractures). All participants received elemental calcium 500mg/day. The primary outcome measure was percent change in lumbar spine BMD. Secondary outcome measures included percent change in femoral neck and trochanter BMD and biochemical indices of bone turnover. Fracture outcomes were monitored as part of adverse event monitoring. No significant differences in fracture outcomes were noted between treatment groups (3 in the placebo and 1 in each of the other treatment groups). All treatment groups were similar to placebo with regard to both the overall safety profile and upper gastrointestinal adverse events. The incidence of upper GI adverse events was 12.9% for alendronate and 14.1% for placebo.

Liberman et al.⁸⁰ conducted a three-year, multi-national, double-blind, placebo-controlled RCT to determine the efficacy of alendronate on bone mass and fracture outcomes in postmenopausal women affected by osteoporosis. A total of 994 postmenopausal women (87.4% Caucasian, 0.4% Black, and 12.2% other), between 45-80 years of age, with lumbar spine BMD ≥ 2.5 SD below the mean value in premenopausal Caucasian women were randomized to one of four treatment groups: placebo or

alendronate 5, 10 or 20mg/day (20mg/day group switched at year 2 to 5mg/day). Evidence of previous vertebral fractures was not an entry criterion (approximately 20% of each treatment group had a previous vertebral fracture). All of the participants received elemental calcium 500mg/day. The primary outcome measures included the percent change in BMD at the spine, femoral neck, trochanter, forearm, and total body, the effect on calcium-regulating hormones, the effect on biochemical indices of bone turnover, and the safety and tolerability of alendronate. Secondary outcome measures included incidence of vertebral fractures, progression of vertebral deformities, height loss, and symptomatic non-vertebral fractures. The definition of an incident of vertebral fracture was a reduction of at least 20%, with absolute decrease of at least 4 mm, in height of any vertebral body between baseline and follow-up. There was a significant difference ($p = 0.03$) in new vertebral fractures (RR, 0.52; 95% CI, 0.28 to 0.95) for the combined alendronate groups. This decreased risk was apparent when stratified by age (under or over 65 years) or the presence or absence of previous vertebral fracture. There was a trend towards, but not a statistically significant difference in, reduced non-vertebral fractures in the alendronate group (estimated risk, 0.79; 95% CI, 0.52 to 1.22). All treatment groups were similar to placebo with regard to both the overall safety profile and upper gastrointestinal adverse events. Of those in the placebo group, 6.0% withdrew owing to adverse clinical adverse events, compared to 5.4% of those taking alendronate. Rates of upper GI adverse events leading to withdrawal were similar to placebo (alendronate 3.5%, placebo 2.0%).

Black et al.⁴² conducted the Fracture Intervention Trial (FIT) in women with pre-existing vertebral fractures, a 2.9-year, multicenter, double-blind, placebo-controlled RCT, to evaluate the effect of alendronate on the risk of morphometric as well as clinically evident fractures in postmenopausal women with low bone mass. A total of 2,027 postmenopausal women (97% Caucasian, 1% Asian, and 1% African-American), between 55-81 years of age, with femoral neck BMD > 2.1 SD below peak bone mass and a previous vertebral fracture, were randomized to either placebo (n=1,005) or alendronate 5mg [(n=1,022); dose increased to 10mg at third year]. All patients with estimated calcium intake at baseline less than 1,000mg daily (82%) received daily elemental calcium 500mg + 250IU vitamin D. The primary outcome was the incidence of new vertebral fractures. Secondary outcomes included clinical fractures (non-vertebral and symptomatic vertebral fractures), changes in height, BMD of the hip, spine, and total body, and changes in biochemical markers of bone turnover. The definition of an incident of vertebral fracture was a reduction of at least 20%, with an absolute decrease of at least 4 mm in height of any vertebral body between baseline and follow-up.

The results of the study revealed a significant difference ($p < 0.001$) in morphometric vertebral fractures with alendronate (RR, 0.53; 95% CI, 0.41 to 0.68). This difference was consistent regardless of age, BMD, number of pre-existing fractures, or history of postmenopausal fracture. The RH of clinically apparent vertebral fractures was 0.45 (95% CI, 0.27 to 0.72). The RH of any clinical fracture was 0.72 (95% CI, 0.58 to 0.90). The RR of any non-vertebral fracture was 0.80 (95% CI, 0.63 to 1.01), hip 0.49 (95% CI, 0.23 to 0.99), wrist 0.52 (95% CI, 0.31 to 0.87), and other 0.99 (95% CI, 0.75 to

1.31). No difference was observed in the rate of adverse events between the alendronate and placebo groups. The overall percentage of women who discontinued treatment due to an adverse event was 7.6% in the alendronate group and 9.6% in the placebo group. Upper gastrointestinal events were experienced by 41.3% in the alendronate group and 40.0% in the placebo group.

Bone et al.⁸¹ conducted a two-year, multicenter, double-blind, placebo controlled, RCT to evaluate dose-response relationships for alendronate in osteoporotic elderly women. A total of 359 postmenopausal women between 60-85 years of age (two thirds 70-85), with lumbar spine BMD ≥ 2.0 SD below mean peak levels, were randomized to one of four treatment groups: placebo; alendronate 1mg/day; alendronate 2.5mg/day; or alendronate 5mg/day. Evidence of more than one lumbar crush fracture was an exclusion criterion. All patients received elemental calcium 500mg/day. The primary outcome measure was lumbar spine BMD. Secondary outcome measures included biochemical indices of bone turnover and mineral metabolism, bone histomorphometry, and vertebral and non-vertebral fractures. The definition of an incident of vertebral fracture was a reduction of at least 20% in height of any vertebral body between baseline and follow-up. Alendronate did not achieve a statistically significant reduction in new vertebral fractures, but did for non-vertebral fractures at doses of 2.5 and 5mg. Alendronate for all doses was well tolerated at all doses. There was no significant difference between treatment and placebo groups in terms of adverse effects which were suspected to be drug related (19.8% in the alendronate group, 23.1% in the placebo group).

Cummings et al.⁸² conducted the 4.2-year, multicenter, double-blind, placebo-controlled RCT, Fracture Intervention Trial (FIT) in women without pre-existing vertebral fracture to determine whether alendronate reduced the risk of clinical fractures in postmenopausal women who have low BMD but no vertebral fracture. A total of 4,432 postmenopausal women (97% Caucasian), between 55-80 years of age, with femoral neck BMD of 0.68 g/cm² were randomized to either placebo (n=2,218) or alendronate 5mg [(n=2,214); dose increased to 10mg at the third year because other trials suggested that 10mg/day had greater effects on BMD without increasing adverse events]. A femoral neck BMD of 0.68 g/cm² was originally thought to correspond to a BMD value of at least 2 SD below mean of normal young adult Caucasian women; however, it was later determined to correspond to only 1.6 SD. Consequently, about one-third of the population had higher BMD than expected. All patients with estimated calcium intake at baseline less than 1,000mg daily (82%) received daily elemental calcium 500mg + 250IU vitamin D. The primary outcome measure was the incidence of clinical fractures (both vertebral and non-vertebral). Secondary outcomes included: new vertebral fractures (morphometrically diagnosed); changes in height; changes in BMD of hip, spine, radius, and total body; and changes in biochemical indices of bone metabolism. The definition of an incident of vertebral fracture was a reduction of at least 20%, with absolute decrease of at least 4 mm, in height of any vertebral body between baseline and follow-up.

The results of the study revealed that alendronate only significantly reduced the risk of clinical vertebral fractures in women with initial T-scores of -2.5 or less (RR,

0.50; 95% CI, 0.31 to 0.82) but not in those with T-score greater than -2.5. Alendronate significantly reduced the risk of morphometric vertebral fractures (RR, 0.56; 95% CI, 0.39 to 0.80). The RH of any clinical fracture (RH, 0.86; 95% CI, 0.73 to 1.10), non-vertebral fracture (RH, 0.88; 95% CI, 0.74 to 1.04), hip (RH, 0.79, 95% CI, 0.43 to 1.44), wrist (RH, 1.19, 95% CI, 0.87 to 1.64), was not statistically significant; other (RH, 0.79, 95% CI 0.65 to 0.96) was statistically significant. However, when results were stratified by BMD at entry, alendronate significantly reduced the risk of clinical fractures in women with an initial T-score of -2.5 or less (RH, 0.64; 95% CI 0.50 to 0.82). There were no significant differences between groups in regards to adverse events; 9.9% of women in the alendronate group and 10.2% of women in the placebo group discontinued study medication because of adverse events. Likewise, 47.5% of women in the alendronate group and 47.2% in the placebo group experienced upper gastrointestinal problems.

Lindsay et al.⁸³ conducted a one-year, multicenter, double-blind, placebo-controlled RCT in postmenopausal women to evaluate the effect on BMD of adding alendronate to ongoing HRT. A total of 428 postmenopausal women, at least 40 years of age (25 years of age if surgically postmenopausal), receiving HRT for at least one year before study entry, with a BMD measurement at the lumbar spine or femoral neck at least 2 SDs below the mean for a reference population of young women (BMD at the other site had to be at least 1.5 SD below the mean), were randomized to receive either 10mg of alendronate/day or placebo along with previously prescribed HRT. All patients with estimated calcium intake at baseline less than 1,000mg daily received daily elemental

calcium sufficient to meet the 1,000mg/day requirement. All patients received vitamin D 400IU/day. The primary outcome measure was the mean percent change in lumbar spine BMD. Secondary endpoints included mean percent change in BMD of the hip trochanter and femoral neck. Data on symptomatic fractures were recorded as adverse events. No symptomatic vertebral fractures were identified in either group. Non-vertebral fractures were more common in the alendronate group, but the difference was not statistically significant. The overall incidence of any clinical adverse event was similar in each group. Approximately 4% of patients in the alendronate group and 7% of patients in the placebo group discontinued study drug due to adverse events. The incidence of gastrointestinal events was identical in both groups (10.7%).

Pols et al.⁸⁴ conducted a one-year, multicenter, double-blind, placebo-controlled RCT in postmenopausal women (94% Caucasian) to evaluate the efficacy and tolerability of alendronate in a population of women with low bone mass. A total of 1,908 postmenopausal women, ≤ 85 years of age, with a BMD of the lumbar spine at least 2 SD below the mean for mature, premenopausal women were randomized to receive either alendronate 10mg/day ($n = 950$) or placebo ($n = 958$). All patients received elemental calcium 500mg/day. The primary outcome measure was lumbar spine BMD. Secondary outcomes included biochemical markers of bone turnover and clinical non-vertebral fracture. The incidence of clinical non-vertebral fractures was significantly lower in the alendronate group ($p = 0.021$), with a RH of 0.53 (95% CI, 0.30 to 0.90). Alendronate was generally well tolerated. No statistically significant differences between treatment groups were found in the overall incidence of adverse events. The incidence of adverse

events resulting in discontinuation of study medication was similar (alendronate 6.4%; placebo 5.6%). There were no significant differences between treatment groups in the overall incidence of upper gastrointestinal adverse events (alendronate 21.3%; placebo 19.3%).

Hormone Replacement Therapy

In all, only three trials⁸⁶⁻⁸⁸ met the inclusion criteria but another recently published trial, the Women's Health Initiative (WHI),⁸⁹ was included in the review given its significant contribution to HRT research. Prior to the WHI,⁸⁹ the methodological rigor that had been applied to clinical trials of fracture prevention of bisphosphonates had not been equally applied to estrogens, which is evident by size and duration of trial. The three trials included in this review were similar in that in each of the studies: Caucasian postmenopausal women with a primary osteoporosis or osteopenia with at least one previous vertebral fracture were enrolled; the trial populations were small (< 130 participants); the mean age was similar (range 58 – 64.9); and the participants were provided elemental calcium and/or vitamin D in comparable doses. The studies differed in the duration of the HRT intervention and doses used. The duration of trials ranged from one-year⁸⁷ to four-years.⁸⁸ The study doses of HRT were different in each study (Transdermal 17 β estradiol, 0.1mg on days 1-21 + oral medroxyprogesterone acetate, 10mg, on days 11-21 of 28-day cycle;⁸⁷ conjugated estrogens, 0.625mg/day, for 25 days/month + medroxyprogesterone, 10mg/day, on days 15-25;⁸⁶ conjugated estrogen, 0.625 mg/day + Norgestrel® 150 μ g/day, for 12 days/month⁸⁸). Vertebral fractures were reported as a secondary outcome in two trials,^{86, 88} and in one study no differentiation

was made between primary and secondary outcomes.⁸⁷ Only one study reported non-vertebral fractures as a secondary outcome.⁸⁸ The criterion used to define incident of vertebral fracture varied between the three studies.

The number of patients with vertebral fractures was reported in one study⁸⁷ and the number of patients with non-vertebral fractures was reported in another study.⁸⁸ The results from these two studies only provide evidence of a trend for a reduction in the relative risk of vertebral fracture (RR, 0.583, 95% CI, 0.262 to 1.301) but no evidence of a reduction in the relative risk of non-vertebral fracture (RR, 1.00; 95% CI (0.068 to 14.795).

Only two trials^{86, 87} provided information regarding the safety and tolerability of HRT. Reported HRT adverse events, which differed significantly from placebo, included: pelvic congestion, cyclic bleeding, and breast tenderness. Brief reviews of the three clinical trials are provided below, followed by a discussion of the WHI⁸⁹ trial.

Pacifici et al.⁸⁶ conducted a 2-year, open label RCT in postmenopausal women to evaluate the effects of phosphate and etidronate versus sequential HRT on axial and appendicular bone mass in osteoporotic women. A total of 128 Caucasian osteoporotic women, between 26-80 years of age with at least one non-traumatic vertebral fracture and/or spinal demineralization were randomized to one of three treatment groups: cyclical K-phosphate and etidronate, cyclical estrogen + progesterone, or placebo. All participants received elemental calcium 1,000mg/day. The primary outcome measure was bone mineral content. Secondary outcome measures included vertebral fractures, biochemical indices of bone turnover, and height loss. The definition of an incident of a

compression vertebral fracture was a reduction of at least 15% in posterior height of any vertebral body compared with mean of the posterior height of the nearest intact vertebrae. Wedging and biconcave fractures were defined by a loss of anterior and central height greater than 20% compared with the posterior height of the same vertebrae. The number of new vertebral fractures was almost identical in all three treatment groups; however, the HRT group had significantly less height loss than the other two groups ($p < 0.05$). Significant side effects (pelvic congestion and cyclic bleeding) occurred only in the HRT group.

Lufkin et al.⁸⁷ conducted a 1-year, double-blind, placebo-controlled RCT in postmenopausal women to evaluate the efficacy of transdermal estradiol therapy in postmenopausal women with vertebral fractures. A total of 75 postmenopausal women, between 47-75 years of age, with BMD of the lumbar spine and proximal femur below the 10th percentile of premenopausal women and one or more vertebral fractures ($\geq 15\%$ reduction in vertebral height) were randomized to either estrogen plus medroxyprogesterone ($n = 36$) or placebo ($n = 39$). Outcome measures included BMD, biochemical indices of bone turnover, bone histomorphologic values, and fracture occurrence. The definition of an incident of vertebral fracture was a reduction of at least 15% in height of any vertebral body between baseline and follow-up. After one year, the estrogen group had significantly fewer new morphometrically diagnosed vertebral fractures ($RR = 0.39$; $p = 0.04$). No report was offered regarding the incidence of non-vertebral fractures. Adverse events experienced by participants in the estrogen arm which differed significantly from placebo included breast tenderness (estrogen 56%;

placebo 5%), endometrial hyperplasia (estrogen 8%; placebo 0%), and all women with intact uteri experienced menstrual bleeding associated with estrogen and progestin.

Wimalawansa et al.⁸⁸ conducted a four-year, open-label RCT in Caucasian postmenopausal women to evaluate whether there is an added beneficial effect on BMD when HRT is combined with cyclical etidronate in women with established osteoporosis. A total of 72 postmenopausal women, 58-72 years of age, with a BMD of the lumbar spine at least 2 SD below the mean of a 35-year old premenopausal women, with at least one morphometrically diagnosed (but no more than four) atraumatic thoracic vertebral crush fractures were randomized to one of four treatment groups: placebo, HRT, etidronate, or the combination of HRT and etidronate. All participants received elemental calcium 1,000mg and 400 IU of vitamin D. The primary outcome measure was BMD. Secondary outcome measures included biochemical indices of bone turnover, vertebral and non-vertebral fractures, and height loss. A new vertebral fracture was defined as a reduction of 20% or more in vertebral height plus a reduction of 15% or more in area in previously unaffected vertebrae. Further deterioration in height or area of previously affected vertebrae was not considered a new fracture. There was no statistical difference in vertebral or non-vertebral fractures, which was primarily thought to be due to the low power of the study. Five of the study participants withdrew from the study due to HRT related side effects.

The WHI⁸⁹ estrogen-plus-progestin trial was the first randomized clinical trial to demonstrate that HRT reduces the risk of hip, wrist, and vertebral osteoporotic fractures. However, the trial was stopped after a mean of 5.2 years (three-years early) because the

test statistic for invasive breast cancer exceeded the stopping boundary and a global index statistic (a nominally significant 15% increase) supported the notion that risks exceeded benefits.⁹⁰ For this reason, investigators determined that HRT should not be used for the prevention of osteoporotic fractures in women without vasomotor symptoms. The WHI estrogen-only trial is ongoing, with completion anticipated in 2005. A brief review of the WHI is provided below.

The WHI⁸⁹ was a 5.6-year (average follow-up), multicenter, double-blind, placebo controlled, RCT to evaluate the effect of estrogen plus progestin on multiple chronic diseases in older women. Cauley et al.⁸⁹ report on the final analysis of fracture endpoints and tested hypotheses that relative risk reductions differed by risk factors for fracture and that the risk-benefit profile of treatment differed across tertiles of fracture risk. A total of 16,608 postmenopausal women (with intact uterus), 50-79 years of age were randomized to one of two treatment groups: placebo (n = 8,102) or conjugated estrogen (0.625mg) plus medroxyprogesterone acetate (2.5mg), in a single tablet, (n = 8,506). BMD measurements were collected in only three of the 40 U.S. clinical centers, where only 4% of the women in the estrogen plus progestin arm and 6% in the placebo arm were considered to have osteoporosis at the total hip using World Health Organization (WHO) criteria.⁹¹ The outcome measures included clinical osteoporotic fractures, BMD [for a subset of women (n = 1,024)], and global index of risk-benefit profile. Estrogen plus progestin significantly reduced clinical vertebral fractures by 34% and hip fractures by 33% (RH, 0.67; 95% CI, 0.47 to 0.96) and total osteoporotic fractures by 24% (RH, 0.76; 95% CI, 0.69 to 0.83). The effect did not differ by risk

factors for fracture. The HR for the global index did not differ across tertiles of fracture risk. Given the unfavorable risk-benefit profile and the availability of safer alternatives for the prevention and treatment of osteoporosis related fractures, researchers concluded that HRT should not be recommended for the prevention and treatment of osteoporosis in women without vasomotor symptoms. The specific HRT related adverse events were not reported.

Combination of Alendronate and Hormone Replacement Therapy

In all, only two trials^{83, 92} met the inclusion criteria. In both clinical trials, the primary outcome measured was the percent change in BMD of the spine and/or hip. Compared with HRT alone, as with earlier trials of HRT, neither of the two clinical trials had sufficient power to establish whether combination therapy has greater anti-fracture efficacy.

Bone et al.⁹² conducted a two-year, multicenter, double-blind, placebo-controlled RCT in postmenopausal osteoporotic women to evaluate the efficacy, safety, and tolerability of combined alendronate and HRT. A total of 425 postmenopausal women (92% Caucasian), 42-82 years of age, with a prior hysterectomy and a mean BMD of the lumbar spine 2.5 SD below the normal reference young adult were randomized to one of four treatment groups: placebo/placebo, alendronate/placebo, conjugated equine estrogen (CEE)/placebo, alendronate/CEE. All participants received elemental calcium 500mg/day. Primary outcome measures were: BMD of the spine, femoral neck, femoral trochanter and total hip; biochemical indices of bone turnover; bone histomorphometry; and safety and tolerability. Secondary outcome measures included fractures, which were

reported as part of adverse event reporting. There was no significant difference in the rate of fracture among the groups. In fact, reported fractures, for the most part, were non-vertebral, due to trauma, and occurred at sites which are not typically considered to be osteoporotic fractures. The tolerability of the alendronate and CEE combination was consistent with those of the individual treatments. Upper gastrointestinal events resulting in discontinuation of study drug occurred with similar frequency among the four treatment groups (alendronate (1%), placebo (0%), CEE (2%), combination (1%)). The CEE treatment was frequently associated with complaints of breast pain and weight gain.

ECONOMIC ASSESSMENT OF HORMONE REPLACEMENT THERAPY AND ALENDRONATE IN THE PREVENTION OF OSTEOPOROTIC FRACTURES

The following is a review of literature regarding the economic evaluation of hormone replacement therapy and alendronate in the prevention of osteoporotic fractures. This literature review includes articles published from 1980 to present. The first section is a review of the literature regarding the economic evaluation of hormone replacement therapy. A review of the literature regarding the economic evaluation of alendronate in the prevention of osteoporotic fractures is provided in the following section. The last section provides a review of three studies that examined the cost-effectiveness of both HRT and alendronate along with other osteoporosis agents.

Pharmacoeconomic Analyses of Hormone Replacement Therapy

A total of 18 economic evaluations of hormone replacement therapy (HRT) were found, ten⁹³⁻¹⁰² were cost-utility analyses (CUAs), six¹⁰³⁻¹⁰⁸ were cost-effectiveness analyses (CEAs), one¹⁰⁹ was a cost-minimization analysis (CMA), and one was a cost-benefit analysis (CBA).¹¹⁰ The conclusions from these studies suggest that in most

instances HRT was cost-effective and compared favorably with other widely accepted clinical practices determined to be cost-effective, such as treatment of hypertension. More specifically, the studies provided evidence that HRT was more cost-effective in symptomatic women;^{93, 98, 99, 102} in women with a hysterectomy;^{93, 97, 99, 102} in the secondary prevention of fracture, in older women, in women with low BMD, or otherwise at increased risk of an osteoporotic fracture;^{93, 101, 105} and when used for longer durations of therapy.^{95, 98, 99, 103, 105}

Bone density screening followed by HRT was assessed in six studies.^{96, 105, 107-110} Three^{96, 107, 109} of the six studies concluded that targeting HRT treatment at high-risk patients via BMD screening was more cost-effective than not screening. However, these studies did not incorporate any of the non-skeletal effects of HRT. One study¹⁰⁵ found unfavorable cost-effectiveness ratios for BMD screening followed by HRT. Another study¹¹⁰ concluded that BMD screening did not meet the pre-established cost-benefit ratio of one. Another study¹⁰⁸ concluded that BMD screening was a cost-effective strategy of targeting patients at a high risk of osteoporotic fracture when annual treatment costs did not exceed \$91 (1995\$).

The cost-effectiveness of HRT in these economic evaluations was influenced by many factors such as age, bone mass, uterus status, presence of menopausal symptoms, duration of intervention, and methods of costing. However, the most significant differences between the economic evaluations can be attributed to the economic model employed to capture the skeletal and non-skeletal health effects of HRT, along with their associated quality-of-life adjustments.

Each economic evaluation employed a slightly different economic model using different estimates of the risk of fracture in the population, HRT's anti-fracture efficacy and relative risk of non-skeletal health effects. For the most part, the incidence of fracture in the population of interest was obtained from epidemiological surveys specific to that population. Since the time when these studies were performed, no RCT of HRTs anti-osteoporotic fracture efficacy had been conducted, each economic evaluation's estimate of HRT's efficacy was based upon the best epidemiological information available at the time. The estimates of HRT's efficacy used in the economic evaluations differed in both magnitude and duration of effect. Each economic model also attempted to account for the significant non-skeletal effects of HRT (increased risk of endometrial cancer, breast cancer and potential cardiovascular benefits, etc.), which were also based upon the best available epidemiological evidence at the time. As a result, there were significant differences between the economic evaluations in regards to which non-skeletal health effects were included in the economic model, the magnitude of the risk estimate for each non-skeletal health effect, and the duration of the non-skeletal health effect risk. The selective inclusion/exclusion of certain non-skeletal health effects associated with HRT significantly impacted the overall cost-effectiveness of HRT in the prevention of osteoporotic fractures. Table 1.4 provides a list of the health effects included in each study, the magnitude of health effect risk estimates, and the duration of health effect risks for 15 of the 18 economic evaluations. The economic evaluations by van der Loos et al.,¹⁰³ Clark and Shuttinga,¹⁰⁹ and Francis et al.¹⁰⁴ were not included due to either limitations in information available or study design.

Table 1.4 Health effect assumptions for HRT

Study	Breast Cancer (Relative Risk)	Cardiovascular Disease (Relative Risk)
Weinstein ⁹³	NI	NI
Weinstein/Schiff ⁹⁴	1.25; applies 5yrs after initiation of tx, continues 5yrs post tx	NI
Weinstein/Tosteson ⁹⁵	1.25	NI
Tosteson et al. ⁹⁶	NI	NI
Tosteson/Weinstein ⁹⁷	ERT: 1.36 after 2yrs of tx + 2yrs post tx cessation; PERT: 1.0	ERT: 0.5; PERT: 1.0
Cheung/Wren ⁹⁸	NS	Varied from 0.5 to 1.0
Daly et al. ⁹⁹	ERT & PERT: 1.3 after 10yrs of use; after tx cessation, risk remains elevated for period equal to tx period	ERT: 0.75 after 5yrs, 0.5 after 10yrs, after tx cessation protective effect remains for period equal to tx period; effect is halved for PERT
Tosteson ¹⁰⁰	ERT: 1.30; PERT: 1.0-2.0	ERT: 0.64; PERT: 0.64 – 0.8
Geelhoed/Harris ¹⁰¹	Risk rate: 1.02 ⁿ , so RR at 15yrs was 1.30	ERT: 0.5
OTA ¹⁰⁵	ERT: 1.35 after 10yrs of tx and remains elevated post cessation of tx; PERT: 1.0	ERT: 0.5 for the duration of tx, returns to 1.0 after cessation of tx; PERT: 0.8
Torgerson et al. ¹⁰⁶	NI	NI
Ankjaer-Jensen/Johnell ¹⁰⁷	1.30; two assumptions: 1) linear increased risk, 2) no increased risk until after 10yrs of tx; effect persists 10yrs post cessation of tx	Optimistic assumption: 0.5; Pessimistic assumption: 0.65
Norlund ¹¹⁰	NI	NI
Daly et al. ¹⁰²	ERT & PERT: 1.3 after 10yrs of use; after tx cessation, risk remains elevated for period equal to tx period	ERT: 0.75 after 5yrs, 0.5 after 10yrs, after tx cessation protective effect remains for period equal to tx period; effect is halved for PERT
Visentin et al. ¹⁰⁸	NI	NI

* Abbreviations: ERT: estrogen replacement therapy; PERT: progesterone and estrogen replacement therapy; NI: not included; NS: not specified; tx: treatment; yrs: years

Table 1.4 Health effect assumptions for HRT (continued)

Study	Cholecystectomy (Relative Risk)	Endometrial Cancer (Relative Risk)	Endometrial Hyperplasia (Relative Risk)
Weinstein ⁹³	2.5 applies 5yrs after initiation of tx to 5yrs post tx cessation	ERT: 0.0 for first 5yrs of tx, then 8.0 until tx cessation + 5yrs	NI
Weinstein/Schiff ⁹⁴	2.5 applies 5yrs after initiation of tx to 5yrs post tx cessation	ERT: 4.0 for first 5yrs of tx, then 8.0 until tx cessation, then 4.0 5yrs post tx cessation; PERT: 1.0	ERT: 9%; PERT: 1.5% for first 5yrs of tx
Weinstein/Tosteson ⁹⁵	NI	ERT: 4.0 for first 5yrs of tx, then 8.0 until tx cessation, then 4.0 5yrs post tx cessation; PERT: 1.0	ERT: 6.0 for first two years of tx; PERT: 1.0
Tosteson et al. ⁹⁶	NI	NI	NI
Tosteson/Weinstein ⁹⁷	NI	NI	NI
Cheung/Wren ⁹⁸	NI	ERT: 8.0; PERT: 2.0	ERT: 9.0%; PERT: 1.5%
Daly et al. ⁹⁹	NI	Non-hysterectomized women/ERT: 6.0 after 5yrs, normal 5yrs after tx cessation; PERT: 1.0	NI
Tosteson ¹⁰⁰	NI	NS	NI
Geelhoed/Harris ¹⁰¹	NI	8.0	NI
OTA ¹⁰⁵	ERT & PERT: 2.5	ERT: > 10yrs 3.5, < 10yrs 7.0, returns to 1.0 after tx cessation	NI
Torgerson et al. ¹⁰⁶	NI	NI	NI
Ankjaer-Jensen/Johnell ¹⁰⁷	NI	NI	NI
Norlund ¹¹⁰	NI	NI	NI
Daly et al. ¹⁰²	NI	Non-hysterectomized women/ERT: 6.0 after 5yrs, normal 5yrs after tx cessation; PERT: 1.0	NI
Visentin et al. ¹⁰⁸	NI	NI	NI

* Abbreviations: ERT: estrogen replacement therapy; PERT: progesterone and estrogen replacement therapy; NI: not included; NS: not specified; tx: treatment; yrs: years

Table 1.4 Health effect assumptions for HRT (continued)

Study	Fracture (Relative Risk)	Nursing Home (Relative Risk)
Weinstein ⁹³	Untreated vs. treated: 3.0 during tx, 2.0 post tx for period equal to tx, then 1.0	NI
Weinstein/Schiff ⁹⁴	ERT & PERT: 0.8 for 5yrs, then 0.4 after tx cessation, protective effect remains for period equal to tx period	NI
Weinstein/Tosteson ⁹⁵	Determined by Melton's ³⁹ logistic regression model; no bone loss during tx, then returned to rate at age 50	Age specific probabilities of discharge post fracture
Tosteson et al. ⁹⁶	Determined by Melton's ³⁹ logistic regression model; no bone loss during tx, then returned to rate at age 50	Age specific probabilities of discharge post fracture
Tosteson/Weinstein ⁹⁷	Determined by Melton's ³⁹ logistic regression model; no bone loss during tx, then returned to rate at age 50	Age specific probabilities of discharge post fracture
Cheung/Wren ⁹⁸	ERT & PERT: 0.8 for the first 5yrs of treatment, and 0.4 thereafter	NI
Daly et al. ⁹⁹	ERT & PERT: 0.8 for 5yrs, then 0.4 after tx cessation protective effect remains for period equal to tx period	NI
Tosteson ¹⁰⁰	Melton's logistic regression model ³⁹ ; assumed no bone loss during tx, then returned to rate at age 50	Age specific probabilities of discharge post fracture
Geelhoed/Harris ¹⁰¹	Melton's logistic regression model ³⁹ ; assumed no bone loss with ERT tx; 50% of normal rate with lifestyle intervention	Age specific: 10% at age 75 to 40% over 85 years of age
OTA ¹⁰⁵	Simulation model based on Study of Osteoporotic Fractures on age-specific bone mass and hip fracture rates	NS
Torgerson et al. ¹⁰⁶	0.7	NI
Ankjaer-Jensen/Johnell ¹⁰⁷	Optimistic assumption: 0.5 Pessimistic assumption: 0.75	NI
Norlund ¹¹⁰	0.5	NS
Daly et al. ¹⁰²	ERT & PERT: 0.8 for 5yrs, then 0.4 after tx cessation, protective effect remains for period equal to tx period	NI
Visentin et al. ¹⁰⁸	0.7	NS

* Abbreviations: ERT: estrogen replacement therapy; PERT: progesterone and estrogen replacement therapy; NI: not included; NS: not specified; tx: treatment; yrs: years

Table 1.4 Health effect assumptions for HRT (continued)

Study	Stroke (Relative Risk)	Uterine Bleeding (Relative Risk)
Weinstein ⁹³	NI	0.036
Weinstein/Schiff ⁹⁴	NI	ERT: 5%; PERT: 2.5%
Weinstein/Tosteson ⁹⁵	NI	NS
Tosteson et al. ⁹⁶	NI	NI
Tosteson/Weinstein ⁹⁷	NI	NI
Cheung/Wren ⁹⁸	NI	ERT: 9% with hyperplasia and 23% without; PERT: 2% with hyperplasia and 12% without
Daly et al. ⁹⁹	ERT: 0.75; PERT: 0.875	NI
Tosteson ¹⁰⁰	NI	NI
Geelhoed/Harris ¹⁰¹	NI	25% the first year, 12.5% the second year
OTA ¹⁰⁵	NI	NI
Torgerson et al. ¹⁰⁶	NI	NI
Ankjaer-Jensen/Johnell ¹⁰⁷	NI	NI
Norlund ¹¹⁰	NI	NI
Daly et al. ¹⁰²	ERT: 0.75; PERT: 0.875	NI
Visentin et al. ¹⁰⁸	NI	NI

* Abbreviations: ERT: estrogen replacement therapy; PERT: progesterone and estrogen replacement therapy; NI: not included; NS: not specified; tx: treatment; yrs: years

Another important factor for determining the cost-effectiveness HRT and an area of significant difference between studies was the quality-of-life (QOL) adjustments employed for HRT and HRT-related health effects. For instance, most studies found HRT to be cost-effective in symptomatic postmenopausal women age ≥ 50 but not in asymptomatic women of the same age. The reason for this is that every woman is affected by a QOL adjustment for HRT and that the consequences occur in the near future; therefore, the effect of discounting is minimal compared to a QOL adjustment for hip fracture, which may occur 30 years into the future. The QOL adjustments for HRT

and HRT-related health effects in each of the CUA economic evaluations were based on expert opinion rather than empirical evidence; therefore, there were also significant differences in QOL adjustments between studies. Table 1.5 provides a list of the QOL adjustments for HRT and HRT related health effects used in the 10 CUAs of HRT.

Table 1.5 QOL adjustments for HRT and HRT related health effects.

Study	Endometrial Cancer	Fracture	Menopausal Symptoms
Weinstein ⁹³	0.8 for 5yrs	0.05	0.99
Weinstein/Schiff ⁹⁴	0.8 for 5yrs	0.9 for life	ERT: 0.99; PERT: 0.995
Weinstein/Tosteson ⁹⁵	0.8 for 5yrs	Nursing home 0.4, disabled but independent 0.8, acute uncomplicated 0.95, post-fracture recovered 1.0	ERT: range 0-2; PERT: range -2 to 2
Tosteson et al. ⁹⁶	NI	Nursing home 0.4, disabled but independent 0.8, acute uncomplicated 0.95, post-fracture recovered 1.0	NI
Tosteson/Weinstein ⁹⁷	NI	Nursing home 0.4, long-term disability 0.8, acute uncomplicated 0.95, disabling hip fracture 0.76, hip fracture requiring nursing home placement 0.36	Consisted of sensitivity analysis
Cheung/Wren ⁹⁸	0.8 for 5yrs	0.9	ERT: 0.99; PERT: 0.995
Daly et al. ⁹⁹	NI	NS	0.95 for severe symptoms; 0.99 for mild symptoms
Tosteson ¹⁰⁰	NI	NS	Considered relief from menopausal symptoms and side effects from PERT
Geelhoed/Harris ¹⁰¹	NI	Nursing home 0.67, acute uncomplicated 0.90	NI
Daly et al. ¹⁰²	NI	NI	NS, but assumed that symptomatic women obtain 5yrs of symptom relief

* Abbreviations: ERT: estrogen replacement therapy; PERT: progesterone and estrogen replacement therapy; NI: not included; NS: not specified; tx: treatment; yrs: years

The following provides a brief review of each individual HRT economic evaluation. Weinstein⁹³ conducted the first pharmacoeconomic analysis of estrogen replacement therapy (ERT). The objective of the study was to determine the cost-effectiveness and cost-utility of ERT in postmenopausal women, particularly for women with an intact uterus and thus at risk for endometrial cancer. A cost-utility analysis was performed from a societal perspective. Weinstein employed a mathematical model in a hypothetical population of postmenopausal women, which was subdivided into three treatment populations: 1) symptomatic menopausal women aged 50 to 60, 2) women with established osteoporosis aged 55 to 70, and 3) asymptomatic postmenopausal women aged 50 to 65. Each treatment population received ERT for either 10 or 15 years. Weinstein used the following cost-effectiveness equation in his mathematical model

$$\frac{C}{E} = \frac{\Delta C_{Rx} + \Delta C_{SE} - \Delta C_{Morb}}{\Delta Y - \Delta Y_{SE} + \Delta Y_{Morb} + \Delta Y_{Symp}}$$

Net resource cost (C) was the sum of the component costs: direct cost of treatment – drugs, physician visits, and routine tests (ΔC_{RX}), costs induced by side effects and complications of treatment (ΔC_{SE}), savings associated with prevention of morbid events – fractures of the hip and wrist (ΔC_{MORB}). Net health benefit (E), measured in life-years-gained or quality-adjusted-life-years, was the sum of the components: the net change in life expectancy (ΔY), the negative quality adjustment associated with side effects and complications of treatment (ΔY_{SE}), the positive quality adjustment associated with prevention of morbid events (ΔY_{MORB}), the positive quality adjustment associated with the relief from menopausal symptoms (ΔY_{SYMP}). The health effects considered in this model included: endometrial cancer, hip and wrist fracture, cholecystectomy, and uterine

bleeding. The assumed relative risks for included health effects are provided in Table 1.4. Risks were based on epidemiological and medical literature and national statistics. Health resource costs were measured in dollars and health benefits were measured in life-years-gained and quality-adjusted-life-years. Quality adjustments were made for illustrative purposes and were specified for the relief of menopausal symptoms, endometrial cancer, and hip fracture. The assumed quality-of-life (QOL) adjustments are provided in Table 1.5. A 5% annual discount rate was applied to all costs and health benefits were calculated both with and without discounting. Weinstein concluded that estrogen treatment was cost-effective in women who have had a hysterectomy and in women with an intact uterus who are at high risk of osteoporosis. The cost-effectiveness in symptomatic women without a prior hysterectomy and at average risk of osteoporosis was dependent upon the subjective importance attached to relief of symptoms.

Weinstein and Schiff⁹⁴ conducted a follow-up to the original study conducted by Weinstein.⁹³ The two primary objectives in this study were: 1) to examine the available evidence in comparing the costs, risks, and benefits of estrogen-progestin (PERT) therapy with ERT, and 2) to update the previous study to account for new epidemiologic evidence on the risks and benefits of ERT (particularly those relating to fractures and breast cancer) and to reflect current economic costs. The principal advantage of PERT was the decreased risk of endometrial hyperplasia and cancer, along with its associated costs of treatment and monitoring. The principal disadvantage of PERT was the subjective inconvenience and discomfort associated with progestin-induced periodic menstrual bleeding. This study adopted the same type of pharmacoeconomic analysis, perspective,

measures of costs and outcomes, discount rate, mathematical model, and methodology used by Weinstein⁹³ in the previous study. In this study, a hypothetical population of postmenopausal women at age 50, with an intact uterus, was subdivided by treatment (ERT or PERT) and treatment duration (5, 10, or 15 years) into six different treatment populations. The health effects considered in this model included: endometrial hyperplasia, uterine bleeding, endometrial cancer, breast cancer, hip and wrist fracture, and cholecystectomy. The assumed relative risks for included health effects are provided in Table 1.4. Risks were based on epidemiological and medical literature. QOL adjustments were made this time to reflect reality (Weinstein's expert opinion) and were specified for the relief of menopausal symptoms, endometrial cancer, and hip fractures. The assumed QOL adjustments are provided in Table 1.5. Weinstein and Schiff concluded that the cost-effectiveness of PERT was comparable to ERT. If no loss of well being is attached to periodic bleeding, then the cost-effectiveness ratios compared favorably with corresponding cost-effectiveness ratios for treatment of moderate diastolic hypertension.

Van der Loos et al.¹⁰³ conducted a pharmacoeconomic analysis of HRT in the prevention of hip fractures. The objective of the study was to determine HRT's cost-effectiveness in hip fracture prevention. They employed a computer simulation model on a hypothetical population of post-menopausal women, which incorporated the relative risks of endometrial cancer, breast cancer, hip fracture, disability requiring nursing home or home care, and death. They assumed that HRT prevents: 55.5% of hip fractures if administered for life or 15.5% if administered for 15 years, 22.6% of home care if

administered for life or 10% if administered for 15 years, and 4.4% of nursing home care if administered for life or 2.2% if administered for 15 years. They estimated a slight gain in life for both 15-year and lifelong treatment durations and a cost/benefit ratio of 1.25 for lifelong administration and a cost/benefit ratio of 1.42 if administered for 15 years. (Abstract, original in French).

Weinstein and Tosteson⁹⁵ conducted a follow-up study of Weinstein and Schiff.⁹⁴ The objective of this study was to update the previous risk-benefit and cost-effectiveness analyses to reflect new epidemiologic and economic evidence. This study followed the same type of pharmacoeconomic analysis, assumptions, and similar data sources of the previous study. The primary piece of new epidemiologic evidence provided was the age-specific incidence rates for hip fracture and its sequelae, which were estimated from a multiple logistic regression model developed by Melton et al.³⁹ Weinstein and Schiff's⁹⁴ mathematical model was applied to a hypothetical population of both symptomatic and asymptomatic postmenopausal women aged 50. Two treatment options were considered, ERT and PERT, for treatment durations of five and 15 years. The health effects considered in this model included: hip fracture, endometrial cancer, endometrial hyperplasia, uterine bleeding, and breast cancer. The assumed relative risks for included health effects are provided in Table 1.4. Risks were based on epidemiologic and medical literature and national statistics. The assumed QOL adjustments are provided in Table 1.5. This study confirmed findings of Weinstein and Schiff⁹⁴ that HRT is cost-effective and has comparable cost-effectiveness to other widely accepted clinical practices. In addition, Weinstein and Tosteson concluded that the cost-effectiveness of PERT relative

to ERT is contingent upon the subjective quality adjustments made for relief of menopausal symptoms and that long-term HRT is more cost-effective than short-term HRT, due to improved prophylaxis against hip fracture.

In 1990, Tosteson et al.⁹⁶ conducted a pharmacoeconomic analysis of bone mineral density (BMD) screening to target hormone replacement therapy (HRT) at women at highest risk of hip fracture. The objective of the study was to determine the costs and benefits of BMD screening for osteoporosis. A cost-utility analysis from a societal perspective was performed. Tosteson et al. employed a Markov state-transition model on a hypothetical population of asymptomatic, perimenopausal, Caucasian women with intact uterus, which were followed from age 50 to 100. The population was subdivided into three treatment populations: 1) no intervention; 2) bone mass measurement at the menopause followed by selective, long-term PERT in women with bone mineral density below a specific threshold; and 3) universal PERT at the menopause. Tosteson evaluated four screening strategies, defined by the bone mineral density threshold (ranging from $< 0.8\text{g/cm}^2$ to $< 1.1\text{ g/cm}^2$) for instituting a 15 year course of (PERT). Tosteson et al. used the following cost-effectiveness equation in the Markov state-transition model

$$\frac{C}{E} = \frac{C_{Rx} + C_{DPA} - \Delta C_{SAVE}}{\Delta LY \text{ or } \Delta QALY}$$

Net resource cost (C) was the sum of the component costs: direct cost of HRT (C_{Rx}), the cost of BMD screening (C_{DPA}), and the economic savings associated with the prevention of hip fracture (ΔC_{SAVE}). The net health benefit (E) was the net change in health outcomes, measured in life-years-gained (ΔLY) or quality-adjusted-life-years ($\Delta QALY$).

Health effects considered in the model only included hip fracture. The assumed relative risks for included health effects are provided in Table 1.4. Risks were based on epidemiologic and medical literature and national statistics. QOL adjustments were made for hip fracture sequelae, which are located in Table 1.5. A 5% annual discount rate was applied to all costs and health benefits. Tosteson et al. concluded that cost-effectiveness ratios for bone density screening with treatment thresholds of < 0.9g/cm² and < 1.0g/cm² were cost-effective in comparison with those reported for generally accepted medical practices, whereas the cost-effectiveness ratio obtained for universal hormone replacement therapy was not cost-effective.

Tosteson and Weinstein⁹⁷ conducted an updated pharmacoeconomic analysis to reflect current medical practice and understanding of the risks and benefits of HRT. The objective of the study was to determine the additional costs and benefits achieved for different management strategies. A cost-effectiveness analysis was performed from a societal perspective. Tosteson and Weinstein employed a Markov state-transition model to a hypothetical population of perimenopausal women. The population was subdivided into two different treatment populations: 1) women with a previous hysterectomy, and 2) women with an intact uterus. Women with a prior hysterectomy received either a 10 or 15 year course of ERT, whereas women with an intact uterus received either a 10 or 15 year course of PERT. The following cost-effectiveness equation was used for the Markov state-transition model

$$\frac{\Delta C}{\Delta(LE_{or}(QALE))} = \frac{\Delta C_{HRT} \pm \Delta C_{NH} \pm \Delta C_{BRCA} \pm \Delta C_{HFX}}{\pm \Delta LE_{HFX} \pm \Delta LE_{BRCA} \pm \Delta LE_{IHD} (\pm \Delta Q_{HFX} \pm \Delta Q_{SYMPT})}$$

Net resource costs (ΔC) are the sum of the component costs: costs of hormone treatment (ΔC_{HRT}), costs of long-term nursing home stays (ΔC_{NH}), costs of breast cancer (ΔC_{BRCA}), and the costs of acute hip fracture (ΔC_{HFX}). The components of net health benefit represent changes in life-expectancy or quality-adjusted-life-expectancy due to changes in hip fracture incidence ($\Delta \text{LE}_{\text{HFX}}$), breast cancer incidence ($\Delta \text{LE}_{\text{BRCA}}$), ischemic heart disease death ($\Delta \text{LE}_{\text{IHD}}$), disability and nursing home residency due to hip fracture (ΔQ_{HFX}), and symptomatic relief from menopausal symptoms or discomfort resulting from hormone replacement therapy (ΔQ_{SYMPT}). The health effects considered in the model included: hip fracture, ischemic heart disease, and breast cancer. The assumed relative risks for included health effects are provided in Table 1.4. Risks were obtained from epidemiologic and medical literature. QOL adjustments were made for hip fracture sequelae and relief of menopausal symptoms. The assumed QOL adjustments are provided in Table 1.5. A 5% annual discount rate was applied to all costs and health benefits. Under base-case model assumptions, Tosteson and Weinstein concluded that the cost-effectiveness ratio for ERT in women with a prior hysterectomy was cost-effective in comparison with those reported for other generally accepted medical practices. In contrast, the cost-effectiveness ratios obtained for PERT in women with an intact uterus was not as cost-effective. The difference in cost-effectiveness ratios between ERT and PERT was primarily attributed to the assumed 50% relative risk reduction in ischemic heart disease with ERT and not with PERT.

Cheung and Wren⁹⁸ conducted a pharmacoeconomic analysis of HRT in an Australian context. The objectives of the study were to determine: 1) the cost-

effectiveness of HRT in comparison to other health care interventions; 2) whether ERT or PERT is more cost-effective; 3) what duration of treatment optimizes cost-effectiveness; and 4) whether it is cost-effective to treat asymptomatic women (with or without prior hysterectomy). A cost-utility analysis was performed from a societal perspective. Cheung and Wren employed a mathematical model, similar to the model used by Weinstein and Schiff,⁹⁴ on a cohort of all New South Wales women age 50 (n=27,021). The treatment alternatives considered were: 1) no intervention, 2) ERT, and 3) PERT for 5, 10, or 15-year durations of therapy. The model examined the effects of three different relative risks (RRs) of dying from myocardial infarction following HRT [1.0 (no cardioprotection), 0.75 (assumed halved cardioprotection with progestin), and 0.5 (assumed cardioprotection offered from ERT)] on treatment, duration of therapy, presence or absence of menopausal symptoms or progestin side effects, and hysterectomy status. The health effects considered in the model included: breast cancer, hip and wrist fracture, myocardial infarction, uterine bleeding, endometrial hyperplasia, and endometrial cancer. The assumed relative risks for included health effects are provided in Table 1.4. Risks were based on epidemiologic and medical literature and national statistics. Health resource costs were measured in Australian dollars and health benefits were measured in life-years-gained and quality-adjusted-life-years. QOL adjustments were the same used by Weinstein and Schiff⁹⁴ except for myocardial infarction which was assigned the same value for hip fracture. The assumed QOL adjustments are provided in Table 1.5. A 5% annual discount rate was applied to all costs and health benefits. Cheung and Wren concluded, under base-case assumptions and a RR of 0.5 of

death from myocardial infarction, that HRT was cost-effective for symptomatic women when compared to other generally accepted medical practices. The cost-effectiveness of HRT in asymptomatic women was contingent upon the cardioprotection associated with HRT. Treatment duration of 15 years was determined to be more cost-effective than treatment durations of 5 and 10 years.

Clark and Schuttinga¹⁰⁹ conducted a pharmacoeconomic analysis of the cost of illness for osteoporotic fractures. The study's objective was to estimate the reduction in cost of illness achieved through BMD screening at the time of menopause and long-term HRT for those most at risk for developing fractures. A cost analysis was performed from the societal perspective. Clark and Schuttinga employed a model in a hypothetical cohort of 100,000 American white women who are BMD screened at age 50 and subsequently stratified into three risk groups: High-risk, Mid-risk, and Low-Risk, with 90% of the High-risk, 70% of the Mid-Risk, and 0% of Low-Risk receiving HRT for 15 years. Health resource costs were measured in dollars, which included not only direct costs but indirect costs (lost productivity). Indirect costs were calculated using the human capital approach. A 6% annual discount rate was applied to all costs. From their model, Clark and Schuttinga estimated a present value reduction in the cost of illness of \$5.1 million (1988\$) for a cohort of 100,000 American Caucasian women, which were followed over a 40-year period beginning in 1988.

In 1992, Daly et al.⁹⁹ performed a pharmacoeconomic analysis of HRT in the British context. The study's objective was to determine the relative benefits of different treatment strategies and what factors most influence cost-effectiveness. They performed

a cost-utility analysis from the perspective of the National Health Service (NHS). Daly et al. employed a computer simulation model in a hypothetical population of postmenopausal women at age 50. The hypothetical population was subdivided into three intervention populations: 1) treatment of hysterectomized women with ERT, 2) treatment of non-hysterectomized women with PERT, and 3) treatment of non-hysterectomized women with ERT. In the standard analysis, each treatment intervention was initiated at 50 years of age and continued for 10 years. The health effects considered in this model included: endometrial cancer, breast cancer, hip fracture, wrist fracture, vertebral fracture, ischemic heart disease, cerebrovascular disease, hysterectomy, and dilatation and curettage. The assumed relative risks for included health effects are provided in Table 1.4. Risks were based on epidemiologic and medical literature and national statistics. Health resource costs were measured in pounds sterling and health benefits were measured in life-years-gained and quality-adjusted life-years. In this study, costs incurred by the NHS of providing health care during extended lifetime were included. QOL adjustments were made for severe menopausal symptoms and for moderate menopausal symptoms. The assumed QOL adjustments are provided in Table 1.5. A 6% annual discount rate was applied to all costs and health benefits were calculated both with and without discounting.

Daly et al. concluded, under model assumptions, that ERT use in symptomatic and asymptomatic women with a prior hysterectomy was more cost-effective than the treatment of hypertension. However, the cost per QALY of PERT for women with mild menopausal symptoms was three times higher than the cost per QALY of ERT in

hysterectomized women with mild menopausal symptoms. Other significant findings by Daly et al. under model assumptions include the life-saving potential of a lasting 50% reduction in cardiovascular disease risk with ERT of almost 2 years and a reduction of approximately 30% in the cost per discounted life year gained when treatment is increased from 10 to 15 years.

Tosteson¹⁰⁰ presented “Hormone Replacement Therapy: Benefit, Risk and Cost Considerations” at the Clinical Therapeutic Conference on Postmenopausal Osteoporosis. Her presentation included an update of the previous cost-effectiveness analysis by Tosteson and Weinstein⁹⁷ to reflect new epidemiologic and economic evidence. She performed a cost-effectiveness analysis from a societal perspective. Tosteson employed the same Markov state-transition model used in the earlier study to follow a hypothetical population of perimenopausal women over time from age 50 to 99. The population was subdivided into two different treatment populations: 1) women with a previous hysterectomy receiving ERT for 15 years, and 2) women with an intact uterus receiving PERT for 15 years. The health effects considered in this model include: endometrial cancer, breast cancer, hip fracture, ischemic heart disease. The assumed relative risks for included health effects are provided in Table 1.4. Risks were based on epidemiologic and medical literature and national statistics. Health resource costs were measured in dollars and health benefits were measured in life-years-gained and quality-adjusted life-years. QOL adjustments for relief from menopausal symptoms and hip fracture were included in the model, but not specified. A 5% annual discount rate was applied to all costs and health benefits were calculated both with and without discounting. Tosteson concluded

that the cost-effectiveness of HRT compares favorably with other generally accepted medical interventions.

Geelhoed and Harris¹⁰¹ performed a pharmacoeconomic analysis to evaluate the overall impact of a public health initiative to treat all postmenopausal women with ERT to prevent hip fracture in an Australian context. The objective of the study was to determine the effects of age of treatment, duration of treatment, and lifestyle intervention on cost-effectiveness of ERT in the prevention of hip fractures. A cost-effectiveness and cost-utility analysis was performed from a societal perspective. Geelhoed and Harris employed a decision analytic tree model based on a Markov process in a hypothetical population of healthy Caucasian women at age 50, differentiated by hysterectomy status prior to age 50. The hypothetical population was further subdivided into four intervention populations: 1) ERT for life beginning at age 50, 2) ERT for 15 years (50-65), 3) ERT for life beginning at age 65, and 4) a lifestyle intervention of calcium supplementation and exercise. The health effects considered in this model include: endometrial cancer, breast cancer, hip fracture, uterine bleeding. The assumed relative risks for included health effects are provided in Table 1.4. Risks were based on epidemiologic and medical literature and Australian national statistics. Health resource costs were measured in Australian dollars and health benefits were measured in life-years-gained and quality-adjusted-life-years, and cost per quality-adjusted-life-years gained. QOL adjustments were made for hip fracture sequelae, which are provided in Table 1.5. A 5% annual discount rate was applied to all costs and health benefits were calculated both with and without discounting. Geelhoed and Harris concluded, under

Health resource costs were measured in pounds sterling and health benefits were measured in averted vertebral fractures. A 6% annual discount rate was applied to all costs and health benefits (averted vertebral fractures). Francis et al. concluded that HRT administered for one-year would reduce the incidence of further vertebral deformation in women with vertebral fractures from 33.7 to 15 per 100 patient-years, with a discounted cost of £138 per averted vertebral fracture. HRT was the most cost-effective intervention of those considered in the analysis and was determined to be cost-effective for the prevention of further vertebral deformation in women with established osteoporosis.

The U.S. Congress Office of Technology Assessment (OTA)¹⁰⁵ conducted a pharmacoeconomic analysis of BMD screening and HRT. The objective of the study was to determine the cost-effectiveness of BMD screening once, at age 50 or 65, and initiation of HRT in those with low bone density. The OTA performed a cost-effectiveness analysis. The perspective of the study was not specifically stated, but can be inferred to be that of a third party (government). The OTA employed a Monte Carlo computer simulation model of a hypothetical population of women eligible for BMD screening and HRT at age 50 and ending either at death or at age 90. The hypothetical population was further subdivided into four intervention populations: 1) BMD screening and HRT for those with low BMD at age 50, 2) Universal treatment at age 50, 3) BMD screening and HRT for those with low BMD at age 65, 4) Universal treatment at age 65. For the BMD screened populations, the OTA evaluated initiation of therapy based on two different BMD treatment thresholds: 1) BMD 1 SD below the young adult reference mean BMD, and 2) BMD below the young adult reference mean BMD. The effects of both ERT and

PERT, with different durations of therapy, were evaluated. The health effects considered in this model included: endometrial cancer, breast cancer, gall bladder disease, hip fracture, cardiovascular disease. The assumed relative risks for included health effects are provided in Table 1.4. Risks were based on epidemiologic and medical literature and national statistics. Health resource costs were measured in dollars and health benefits were measured in life-years-gained. No quality adjustments were included in this study. A 5% annual discount rate was applied to all costs and health benefits were calculated both with and without discounting.

The OTA concluded, under model assumptions, that long-term (40 year) ERT at age 50 with and without BMD screening was cost-effective in comparison with many other interventions currently paid for by public and private third-party payers, with cost per life-year gained ratios of \$27,000 and \$23,000 (1993\$), respectively. The cost per added life year declined substantially as the duration of the intervention increased for all strategies. The OTA confirmed findings of previous studies, that the cost-effectiveness of HRT is extremely sensitive to the assumed relative risk reduction of cardiovascular disease. When the assumed cardio-protective benefit was removed, cost per life-year-gained ballooned to \$155,000 for ERT with BMD screening and \$450,000 for ERT with universal treatment. The cost per added year of life for long-term (40 year) PERT was roughly \$71,000 and roughly the same as ERT for without and with BMD screening, respectively. Due to a lack of evidence on the cardio-protective effect of HRT initiated in women 65 years of age, a relative risk of 1.0 for cardiovascular diseased was assumed.

Therefore, the cost-effectiveness of HRT initiated at the age of 65, regardless of BMD screening or not, was determined not to be cost-effective.

Torgerson et al.¹⁰⁶ authored “Using economics to prioritize research: a case study of randomized trials for the prevention of hip fractures.” The study’s objective was to demonstrate how a combined clinical and economics approach can be used to help prioritize research funds. The ultimate goal of this analysis was to identify which intervention, a priori, research funding ought to be directed towards. A cost-effectiveness analysis was performed. The perspective of the study was not directly identified but assumed to be that of the NHS. Torgerson et al. modeled each treatment alternative (annual vitamin D injection (30,000 IU), thiazide diuretics (50mg HCTZ), HRT, calcium and vitamin D, calcium, calcitonin with calcium and vitamin D) for five years in a cohort of 100,000 women, under the following assumptions: treatment age 80, cohort has the same age related mortality of women in the general population, the annual incidence of hip fractures for women aged ≥ 80 is 2.3%. Health resource costs were measured in pounds sterling and health benefits were measured in averted hip fractures. A 6% annual discount rate was applied to all costs and health benefits. Torgerson et al. concluded that vitamin D injection was most worthy of randomized control trial funding. HRT was considered to be too costly and to have an adverse safety profile (breast cancer, endometrial cancer). Torgerson et al. calculated a cost of £7,398 per averted hip fracture for HRT.

Ankjaer-Jensen and Johnell¹⁰⁷ conducted a pharmacoeconomic analysis of different pharmaceutical programs to prevent osteoporosis from a Danish context. The

objectives of the study were to compare the cost-effectiveness of different pharmaceutical programs to prevent osteoporosis, to determine cost-effectiveness with respect to age of treatment, and to compare the cost-effectiveness of population-based prevention programs with programs targeted at individuals at high risk for fracture identified through BMD screening. This study examined the cost-effectiveness of calcium supplementation, etidronate, and calcitonin. HRT was included as a benchmark. A cost-effectiveness analysis was performed from a societal perspective. Ankjaer-Jensen and Johnell employed a simulation model of a hypothetical cohort of 1,000 50-year old women. The HRT treatment intervention consisted of ERT for 10 years. Two values of cost-effectiveness were produced; one under a set of optimistic assumptions and one under a set of pessimistic assumptions. The following cost-effectiveness equation was employed

$$\frac{C - B}{E}$$

Costs (C) included medication costs, costs of GP visits, and costs of diagnostic tests due to treatment. The effect (E) was the number of hip fractures avoided. The benefit (B) was the change in costs due to wrist, vertebral, and hip fractures averted. For HRT, the model included changes in cost due to changes in incidence of cardiovascular disease and breast cancer. Health effects considered in the model included: wrist, vertebral, and hip fracture, breast cancer, and cardiovascular disease. The assumed relative risks for included health effects are provided in Table 1.4. Risks were based on epidemiologic and medical literature and national statistics. Health resource costs were measured in Danish Kroner (DKK) and health benefits were measured in averted wrist, vertebral, and hip fractures. No QOL adjustments were made. A 5% annual discount rate was applied to

all costs and health benefits were calculated without discounting. Ankjaer-Jensen and Johnell concluded that etidronate was the most cost-effective alternative and calcitonin was the least cost-effective alternative. HRT was not included in the direct comparison, since the extraskeletal effects of HRT were not included in the analysis. The cost-effectiveness of the population-based prevention programs with HRT ranged from DKK - 38,909 (optimistic assumption) to DKK 178,100 (pessimistic assumption). The cost-effectiveness of programs targeted at individuals at high risk for fracture identified through BMD screening with HRT was not reported nor was HRT included in the analysis on the effect of treatment age. However, overall the screening program was found to be more cost-effective than the population-based program for all treatment alternatives.

Norlund¹¹⁰ conducted a pharmacoeconomic analysis of BMD and HRT at the request of the University Hospital of Lund, Sweden to evaluate the proposed solution of BMD screening and HRT to the problem of increasing rates of fractures among elderly women. The objective of the study was to determine the cost-effectiveness of BMD screening and HRT for those patients most at risk and thereby reduce hip, spine, and wrist fractures. A criterion established by the University Hospital board was that the program had to have a cost/benefit ratio of one to be implemented. A cost-benefit analysis was performed from the perspective of the University Hospital of Lund. Norlund employed a computer simulation model for a cohort of 17,000 Swedish women aged 50 to 54, which were followed until the age of 89. A total of 70% of the population was anticipated to be BMD screened and 20% of the screened population was expected to

have low BMD requiring HRT, which was to be administered for seven years. Compliance with HRT was projected to be 30%. HRT's relative risk reduction for fracture was assumed to be 50%. Health effects considered in the model included: wrist, vertebral, and hip fracture. The assumed relative risks for included health effects are provided in Table 1.4. Risks were based on epidemiologic and medical literature and national statistics. Health resource costs were measured in Swedish kronors and health benefits were measure in averted fractures of the wrist, spine, and hip. Norlund included direct and indirect costs in his analysis. A 5% annual discount rate was applied to all costs and health benefits. According to the model, 100 fewer fractures occurred as a result of the preventive program, of which 61 were expected to be hip fractures. However, the benefit-cost ratio was 0.68, therefore the program was not implemented.

Daly et al.¹⁰² conducted a pharmacoeconomic analysis of HRT as an update to the previous analysis in British context. The study's objective was to assess the relative benefits of different treatment strategies, and to identify which factors most influence cost effectiveness. A cost-effectiveness analysis was performed from the perspective of the NHS. Daly et al. employed a computer simulation model in a hypothetical population of postmenopausal women at age 50. The hypothetical population was subdivided into two intervention populations: 1) treatment of women with a previous hysterectomy with ERT, 2) treatment of women with an intact uterus with PERT. In the standard analysis, each treatment intervention was initiated at 50 years of age and continued for 10 years. The health effects considered in this model included: endometrial cancer, breast cancer, hip fracture, wrist fracture, vertebral fracture, ischemic heart disease, cerebrovascular

disease (stroke), hysterectomy, dilatation and curettage. The assumed relative risks for included health effects are provided in Table 1.4. Risks were based on epidemiologic and medical literature and national statistics. Health resource costs were measured in pounds sterling and health benefits were measured in life-years-gained and quality-adjusted-life-years. In this study, costs incurred by the NHS of providing health care during extended lifetime were included. QOL adjustments were made but not specified. A 6% annual discount rate was applied to all costs and health benefits were calculated both with and without discounting. Daly et al. reached the similar conclusions as those reached in their previous study. Treatment of symptomatic menopausal women is cost-effective for any duration of treatment, whereas treatment of non-hysterectomized asymptomatic women is of questionable cost-effectiveness.

Visentin et al.,¹⁰⁸ conducted a pharmacoeconomic analysis of calcitonin to assess the impact of the Italian Health Services removal of calcitonin from the refund list on 1 January 1994. The focus of the analysis was calcitonin but included other osteoporosis medications licensed in Italy. The objective of the study was to determine the cost-effectiveness of calcitonin. A cost-effectiveness analysis was performed from the perspective of the Italian government. Visentin et al. employed Weinstein and Schiff's⁹⁴ mathematical model to hypothetical population of Italian women. In the HRT analysis, the population received either ERT or PERT for one year. In addition, the study examined the cost-effectiveness therapies with BMD screening. The following cost-effectiveness equation was used for Weinstein and Schiff's mathematical model:

$$C_{PAHF} = C_{RX} - N \otimes C_{MORB} + C_{SE} \pm C_{RXLE}$$

Net resource costs per avoided hip fracture (C_{PAHF}) are the sum of the component costs: all direct medical and health care costs of one year's treatment (C_{RX}), the number of people requiring treatment to prevent one hip fracture (N), savings in health care, rehabilitation and custodial costs due to the preventing or alleviation of disease (C_{MORB}), all health care costs associated with the adverse side effects of treatment (C_{SE}), and costs of diseases that would not have occurred if the patient had not lived longer as a result of the original treatment (C_{RXLE}). A zero figure for C_{SE} and C_{RXLE} was assumed. Health effects considered in the model only included hip fracture. Health resource costs were measured in Italian prices and expressed in U.S. dollars and health benefits were measured in averted hip fractures. No QOL adjustments were made. Use of a discount rate was not used since the study only examined costs and benefits incurred in a one-year period. Visentin et al. concluded that not only was ERT cost-effective but it was the most cost-effective of the treatment alternatives considered (calcitonin, bisphosphonates, anabolic steroids, vitamin D metabolites, fluorides, and flavonoid glycosides) for the prevention of hip fractures. PERT was found not to be cost-effective. In addition, Visentin et al. concluded that BMD screening, which identified the lowest quartile for treatment, was cost-effective if annual treatment costs did not exceed \$91 (1995\$).

Pharmacoeconomic Analyses of Alendronate

A total of four¹¹¹⁻¹¹⁴ pharmacoeconomic analyses of alendronate were found, of which three were CUAs^{111, 112, 114} and one was a CEA.¹¹³ Three^{111, 112, 114} of the four studies were similar in that each: examined the cost-effectiveness of alendronate in older postmenopausal women (≥ 65 years of age); who were at an increased risk of

osteoporotic fracture (BMD: 2 to 2.5 SD below mean, or previous vertebral fracture); and the duration of intervention was 5 to 10 years. Under base-case assumptions, each of these studies, found alendronate to be cost-effective. Buckley and Hillner¹¹³ examined the cost-effectiveness of alendronate in the prevention of vertebral fractures in women taking corticosteroids and concluded that alendronate was the most effective and most costly intervention. A brief review of the four studies is provided below.

Kristiansen et al.¹¹¹ conducted a pharmacoeconomic analysis of alendronate in a Norwegian context. The objective of the study was to determine the cost-effectiveness of a five-year alendronate intervention in women aged 65 years with a BMD of the femoral neck 2.5 SD below peak bone mass. A cost-utility analysis was performed and a societal perspective was adopted. Kristiansen et al. used a computer simulation model. The risk of fracture was based on epidemiologic and medical literature. A discount rate was not specified. The discounted cost per quality-adjusted-life year was Norway Kroner (NOK [1 NOK = approximately 0.15 US dollars) 528,000, NOK 291,000, and NOK 147,000 when BMD was 1.5, 2.5, and 3.5 below peak bone mass, respectively. Kristiansen et al. concluded that alendronate was cost-effective when administered to women at high risk of osteoporotic fractures. (Abstract, original in Norwegian).

Coyle et al.¹¹² conducted a pharmacoeconomic analysis of calcitonin from a Canadian context. The objective of the study was to determine the cost-effectiveness of nasal calcitonin in the treatment of postmenopausal women with a previous fracture who either cannot or will not take hormone replacement therapy. Both a cost-effectiveness and cost-utility analysis were performed from the perspective of a provincial government.

A decision analytical framework, based on a Markov process with a cycle length of one-year, was used to determine the cost-effectiveness of calcitonin, alendronate, and etidronate in women with a previous fracture. The base-case analysis looked at treatment durations of five and ten years, initiation of therapy at age 65, 50% compliance after one-year of treatment, and a linear reduction in benefit after cessation of treatment equal to duration of treatment. The efficacy of the treatment alternatives: calcitonin 200IU once daily, alendronate 10mg once daily, and cyclical etidronate (400mg daily for 2 weeks) was obtained from a meta-analysis of randomized controlled clinical trials. One of the inclusion criteria in the meta-analysis was trials with postmenopausal women with either prevalent fractures or a BMD score less than 2 SD below the mean. The health effects considered in the model included: wrist, vertebral, and hip fracture. Risks were based on national statistics. Health resource costs were measured in Canadian dollars and health benefits were measured in averted wrist, vertebral, and hip fractures and quality adjusted life years. Cost estimates included in the model were costs of drug therapy, treatment of drug side effects, and treatment costs of fractures. The following quality adjustments were made for health states post fracture: normal health (0.92), hip fracture first year (0.40), hip fracture following year (0.50), wrist fracture first year (0.90), vertebral fracture first year (0.64), which were obtained from an ongoing study at the Ottawa Hospital. A 5% annual discount rate was applied to costs and health benefits.

Coyle et al. found that the cost-effectiveness of alendronate, in comparison with calcitonin, was dependent upon whether a study by Black et al. was included in alendronate's meta-analysis. The study by Black et al. decreased the cost-effectiveness

of alendronate because one-third of the patients in the randomized clinical trial did not meet the inclusion criteria of prevalent fractures or a BMD score less than 2 SD below the mean, thereby decreasing efficacy. If the study by Black et al. is excluded from the meta-analysis, then alendronate was shown to be more cost-effective than calcitonin and overall was considered to be of moderate cost-effectiveness.

In 1990, Buckley and Hillner¹¹³ conducted a pharmacoeconomic analysis of medications used in the prevention of vertebral fractures in women taking corticosteroids. The objective of the study was to determine the cost-effectiveness of calcium and vitamin D, cyclic etidronate, and alendronate in the prevention of vertebral fractures in women with either normal bone density or osteopenia who initiate moderate dose corticosteroid therapy. A cost-effectiveness analysis was performed from the perspective of the patient or insurer. Buckley and Hillner employed a model in a hypothetical population of Caucasian women, which was divided into the following cohorts based on lumbar spine BMD (LS BMD): aged 30 normal (T-score = 0.0), aged 50 borderline osteopenia (T-score = -1), aged 60 moderate osteopenia (T-score = -1.5), aged 70 severe osteopenia (T-score = -2). The hypothetical cohorts initiated one-year of prednisone treatment at a mean dose of 10mg/day. To prevent corticosteroid induced vertebral fractures, the hypothetical cohort received one of four treatments for one-year: 1) no treatment, 2) calcium (500 - 1000 mg/day) and vitamin D (400 IU/day), 3) cyclic etidronate (400 mg/14 days of every 3 months), and 4) alendronate (10 mg/day). Cost-effectiveness was examined at two endpoints, 10 years after treatment and at age 80. Health resource costs were measure in dollars and health benefits were measured in averted vertebral fractures.

Costs included both direct medical and indirect costs (lost productivity for patient and caregiver). A 3% discount rate was applied to all costs and health benefits were not discounted.

The authors concluded that alendronate prevented the most vertebral fractures but the cost per averted vertebral fracture was high. The marginal cost-effectiveness of alendronate compared to cyclic etidronate at the ten-year point ranged from \$121,125 (LS BMD at age 50, T-score -1) to \$7,883 (LS BMD at age 70, T-score -2) per averted vertebral fracture and at the age of 80 ranged from \$ 4,533 (LS BMD at age 50, T-score -1) to \$7,883 (LS BMD at age 70, T-score -2) per averted vertebral fracture.

Johnell et al.¹¹⁴ conducted a pharmacoeconomic analysis of alendronate for the treatment of osteoporotic women in Sweden. The objective of the study was to determine the cost-effectiveness of alendronate in the treatment of osteoporotic women using data from the FIT trial. A cost-effectiveness analysis was performed from the societal perspective. Johnell et al. employed a Markov model, with a cycle length of one-year, to determine the cost-effectiveness of alendronate for a hypothetical cohort of Swedish women comparable to those in the FIT vertebral fracture arm (i.e., age 71, low bone mass with at least one previous vertebral fracture). In the base-case analysis, women were simulated until the age of 100 or death, the treatment duration was assumed to be five-years, the duration of effect declined linearly over a five-year period following cessation of treatment. The health effects considered in the model included: wrist, vertebral, and hip fractures. Age-specific relative risks for fractures of the wrist, vertebrae, and hip were obtained from Swedish epidemiologic studies. The relative risk reductions of

fracture for patients treated with alendronate were obtained from the vertebral fracture arm of the FIT trial (51% for hip, 55% for vertebral, and 48% for wrist). Health resource costs were initially measured in Swedish kronors then converted to U.S. dollars and health benefits were measured in averted hip fractures, life-years gained, and quality-adjusted-life-years. Both direct medical and non-medical costs were included in the model. The quality of life weights used in the base-case analysis were age-specific and ranged from: [well 0.90 (age 50-64) to 0.63 (75 years +), hip fracture 0.70 (age 50 – 64) to 0.43 (75 years +), spine fracture 0.81 (age 50 – 64) to 0.57 (age 75 years +), wrist fracture 0.86 (age 50-64) to 0.60 (age 75 years +), post-hip fracture 0.80 (age 50-64) to 0.53 (age 75 years +)]. A 5% annual discount rate was applied to costs and health benefits. A threshold for acceptable cost-effectiveness was established as a range between \$20,000 - \$40,000 per QALY gained (1996\$). Johnell et al. concluded that alendronate was “good value for the money” for the treatment of osteoporosis and prevention of fractures. Alendronate met the \$30,000 threshold for acceptable cost-effectiveness for the base-case analysis and for a cohort of somewhat lower risk patients in a sensitivity analysis.

Pharmacoeconomic Analyses of Hormone Replacement Therapy and Alendronate

Three^{2, 85, 115} analyses examined the cost-effectiveness of alendronate and HRT in the same economic evaluation. All three economic evaluations were CUA's. Each analysis concluded that HRT was more cost-effective than alendronate under base-case assumptions. The National Osteoporosis Foundation (NOF) conducted a study to develop a set of evidence and outcomes-based recommendations for the diagnosis and

treatment of osteoporosis in postmenopausal Caucasian women. The study included a pharmacoeconomic analysis of HRT, calcium, vitamin D, calcitriol, calcitonin, bisphosphonates, fluoride, and exercise. A cost-effectiveness analysis was performed from the societal perspective. Since the primary purpose of this study was to develop recommendations for the diagnosis and treatment of osteoporosis and not a pharmacoeconomic analysis, the specific details of the model employed were not available. However, certain assumptions incorporated into the model were described. The age-specific relative risk for fracture of the wrist, vertebrae, and hip were obtained from a model developed by Black et al. based on data obtained from the Study of Osteoporotic Fractures (SOF). Investigators assumed a 50% relative risk reduction for fracture of the hip, wrist, and vertebrae with alendronate and a 50% relative risk reduction for vertebral fracture and a 25% reduction for hip and wrist fracture for HRT. Health resource costs were measured in U.S. dollars and health benefits were measured in quality-adjusted life-years. No discounting was performed. Thirty different quality-of-life weights, developed by the NOF committee, were used in the base-case analysis to account for the QALYs lost due to an event. A threshold for acceptable cost-effectiveness was established at \$30,000 per QALY gained (1998\$). The NOF concluded that overall HRT was the most cost-effective treatment of osteoporosis. The NOF recommended HRT use in women with a hip BMD T score of less than -2 without risk factors and in women with a T score of less than -1.5 with a history of nonvertebral fracture. The NOF recommended that alendronate should be reserved for women only at the highest risk of fracture. The NOF concluded that alendronate is cost-effective for women with hip T

scores below -2.5 without prior history of fracture and for women who have experienced a nonvertebral fracture and who have T scores between -2.5 and -1, depending on age and number of risk factors.

Rosner et al.¹¹⁵ conducted a pharmacoeconomic analysis of both HRT and alendronate in a Canadian context. The objective of the study was to evaluate the cost-effectiveness of multi-therapy treatment strategies in the prevention of vertebral fractures in postmenopausal women with osteoporosis. The multi-therapy treatment strategies were designed to reflect clinical practice where patients are free to decline, accept, and discontinue therapies. A cost-utility analysis was performed from a societal perspective. Rosner et al. employed a computer simulation model in a hypothetical cohort of 1,000 postmenopausal (at least eight years postmenopause) who had established osteoporosis (diagnosed by either a BMD score 2.5 SD below the mean or ≥ 2 vertebral fractures). The number of vertebral fractures which occurred and costs incurred were evaluated every six months over three years for nine different multi-therapy treatment strategies, which were composed of sequentially ordered combinations of five different medications (ERT, PERT, alendronate, etidronate, and calcium). The only health effect incorporated into the model was vertebral fracture (i.e., the non-skeletal effects of HRT were not included). Risks were based on epidemiologic and medical literature and national statistics. The assumed vertebral fracture relative risks reduction for HRT was 0.45 and for alendronate was 0.37. In addition, Rosner et al. incorporated patients' willingness to initiate and continue therapy into the model. Health resource costs were measured in Canadian dollars and health benefits were measured in averted vertebral fractures and

quality adjusted life years. In addition to direct medical costs, Rosner et al. included indirect costs (lost productivity) for patient and caregiver. A 5% annual discount rate was applied to costs and health benefits.

Rosner et al. concluded that the sequential treatment pattern of ERT → calcium → no therapy treatment strategy was most cost-effective. The cost-effectiveness of this treatment strategy fell just below the \$Can20,000/QALY gained threshold, which is a standard that has been applied in other Canadian pharmacoeconomic evaluations indicating strong evidence for program adoption. The ERT → alendronate → calcium → no therapy treatment alternative exceeded the \$Can20,000 - \$Can100,000/QALY threshold, which is a standard that indicates moderate evidence for adoption.

Kanis et al.⁸⁵ conducted a pharmacoeconomic analysis of bisphosphonates, vitamin D, 1-alpha hydroxylated derivatives of vitamin D, calcium, estrogen, estrogen like agents, anabolic steroids, fluoride salts, thiazide diuretics, raloxifene, vitamin K₂, protein supplements, and exercise. The objective of the study was to model the cost-effectiveness of these agents in established osteoporosis from a British context. A cost-utility analysis was performed from a societal perspective. Kanis et al. employed Sheffield Economics Model for Osteoporosis (SHEMO), which is an individual-based, transition state, osteoporosis model created in Excel 97©. The transition states included: fracture states, death from hip fracture, nursing home admission due to hip fracture, fatal and non-fatal CHD, fatal and non-fatal breast cancer, and death from other causes. The model was applied to hypothetical cohorts of postmenopausal women, with established osteoporosis, aged 50, 60, 70, and 80 years of age. The duration of treatments was five

years plus a five-year offset, except for calcium and calcitonin, for which a three-year offset was used (offset = duration for which an effect persists). The annual risk of hip, spine, distal forearm, and humerus osteoporotic fractures was determined from epidemiological data for United Kingdom (UK) women. QOL adjustments were based on a set of reference case health state value (HSV) multipliers developed by Braizer et al.¹¹⁶ which were subsequently applied to population normative data described by Kind et al.¹¹⁷ In addition to fracture, the health effects considered in the model included breast cancer, and coronary heart disease where appropriate (HRT). Health resource costs were measure in pounds sterling. A 6% discount rate was applied to all costs and a 1.5% discount rate was applied to QALYs. Kanis et al. concluded under the base-case assumptions (vertebral fracture (RR, 0.58), no effect appendicular fracture, breast cancer, or CHD), HRT was not cost-effective in women aged 50 but was at 60 years or more. A series of different estimates of cost-effectiveness were obtained when sensitivity analyses were performed on HRT's base-case assumptions: 1) HRT was cost-effective at all ages with hip fracture risk adjustment (RR, 0.86; 95% CI, 0.42 to 1.75); 2) HRT's cost-effectiveness improved when additional protective effects on CHD were included; 3) HRT's cost-effectiveness decreased but remained cost-effective with a breast cancer risk adjustment (RR, 1.35); and 4) HRT's cost-effectiveness improved when risk adjustments were made both for CHD and breast cancer. For alendronate, under base-case assumptions (hip fracture (RR, 0.61), vertebral fracture (RR, 0.54), and humeral fracture (RR, 0.83), the cost-effectiveness of alendronate improved with age and became cost-effective at age 70 years or more.

METHODOLOGY LITERATURE

Net-Benefit Regression Method of Cost-Effectiveness Analysis

A net-benefit regression (NBR) method of cost-effectiveness analysis (CEA) is employed in this research. The net-benefit regression method is a novel approach to a CEA, which incorporates a net-benefit statistic within a standard regression type framework to solve the cost-effectiveness problem. The net-benefit statistic is the product of the net-benefit framework - a reformulation of the traditional cost-effectiveness problem that replaces incremental cost-effectiveness ratios (ICERs), along with their inherent statistical problems, with the net-benefit statistic, along with its more attractive statistical properties. This method of CEA was selected for this analysis for two reasons: 1) it provides the ability to evaluate the importance of covariates on the marginal cost-effectiveness of an intervention, thus allowing the identification of important patient subgroups, and 2) it provides the ability to account for the heterogeneous nature of observational data. Since this methodology is new, the remainder of this sub-section will be devoted to providing an overview of this methodology. This overview is primarily based on Hoch's¹¹⁸ article, which first introduced this new methodology in 2002. This overview will focus on: the problems associated with analyzing ICERs in a stochastic framework; the net-benefit framework approach to cost-effectiveness; the advantages and disadvantage of the net-benefit approach compared to a traditional CEA; the net-benefit regression method approach to cost-effectiveness; and the advantages of the net-benefit regression approach to cost-effectiveness.

To understand the problems associated with the traditional CEA, a review of the fundamental elements of a CEA is appropriate. In a traditional medical CEA, results comparing a new treatment intervention (T_A) with an alternative treatment intervention (T_B) are expressed in the form of an ICER, which compares the incremental cost per change in units of outcome measure:

$$ICER = \frac{\mu_{CA} - \mu_{CB}}{\mu_{EA} - \mu_{EB}} = \frac{\mu_{\Delta C}}{\mu_{\Delta E}}$$

where μ_{CA} , μ_{CB} , μ_{EA} , and μ_{EB} represent the mean cost and effects of interventions A and B, respectively, in the population and $\mu_{\Delta C}/\mu_{\Delta E}$ represents the ICER. Since the true population means are not known, the “estimated” ICER can be estimated using the “analogy” estimator:¹¹⁹

$$IC\hat{E}R = \frac{\bar{C}_A - \bar{C}_B}{\bar{E}_A - \bar{E}_B} = \frac{\Delta\bar{C}}{\Delta\bar{E}}$$

where \bar{C}_k and \bar{E}_k represent sample mean cost and effects of interventions A and B, respectively, and $\Delta\bar{C}/\Delta\bar{E}$ represents the $IC\hat{E}R$ (parameter estimate). In a traditional CEA, a more costly but more effective intervention should be implemented if the ICER of the intervention is below some maximum acceptable willingness to pay:

$$\frac{\mu_{\Delta C}}{\mu_{\Delta E}} < \lambda$$

where λ represents the maximum acceptable willingness to pay per unit gain of health. In the traditional CEA, λ is unknown to the analyst and no attempt is made to address it.

An analysis of uncertainty surrounding the ICER estimate is a key component of any CEA. However, the inability of the traditional CEA to easily manage uncertainty is

well documented in health economic literature.¹²⁰⁻¹²³ Theoretical problems arise in the interpretation of the ICER, in the construction of confidence intervals (CIs) for an ICER probability distribution that covers more than one quadrant of the cost-effectiveness plane (CE), and in the construction and interpretation of CIs for negative ICERs.¹²⁴

The interpretation of an ICER is ambiguous unless it is presented in the context of the quadrant of the cost-effectiveness plane (the CE plane is illustrated in Figure 1.1) to which it corresponds (or if the sign of the numerator and denominator are known). For example, a positive ICER, less than λ , is favorable for intervention A in the NE quadrant, but is unfavorable in the SW quadrant. Likewise, a negative ICER in the SE quadrant is favorable for intervention A, but is unfavorable in the NW quadrant. Of greater concern, is when the joint probability distribution of cost and effects extend to more than one quadrant of the CE plane. In this situation, attempts to construct confidence intervals by employing the bootstrapping methods may lead to misleading confidence limit estimates.¹²⁴ As a result, analysts must often employ the cost-effectiveness acceptability curve approach to summarizing uncertainty.¹¹⁸ Finally, negative ICERs present important complications for the construction and interpretation of CIs. For example, for an ICER distribution in the SE quadrant (intervention A is less costly and more effective) a large magnitude is desirable for both the numerator and the denominator. However, these two desirable features drive the ICER in opposite directions, thus ICER distribution in quadrant II does not lend itself to meaningful interpretation.¹²⁴

model assumptions, that ERT initiated at 65 years of age was the most cost-effective option. This treatment option was superior to ERT for life because the duration of treatment intervention was shorter (less cost), whereas the benefits for hip fracture and heart disease were maintained at the time of peak disease incidence. The cost-effectiveness of ERT for 15 years from the age of 50 was the least cost-effective of the ERT interventions, because the protective effects had subsided by the time of peak disease incidence. The cost-effectiveness of the lifestyle intervention was the least cost effective, because of the high cost of exercise and the relatively low gains in life-years.

Francis et al.¹⁰⁴ conducted a pharmacoeconomic analysis of vertebral fracture prevention strategies. The objective of the study was to determine the cost-effectiveness of different treatment strategies (HRT, cyclic etidronate, and calcitonin) for the prevention of further vertebral fractures in women with a previous vertebral fracture. A cost-effectiveness analysis was performed. The perspective of the study was not specified but can be inferred to be that of the National Health Service (NHS). Francis et al. employed a model that incorporated underlying fracture incidence, effectiveness of intervention, and costs of therapy. The incidence of vertebral fractures was obtained from placebo controlled groups participating in randomized controlled clinical trials of various osteoporosis treatments. The effectiveness of the interventions was gained from their respective controlled clinical trials. From the randomized controlled trials, it was determined that HRT was associated with a 60% reduction of vertebral fractures. Model output was used in the following cost-effectiveness equation

$$\frac{\text{Total discounted costs of treatment} \times 100}{\text{Discounted number of vertebral fractures averted per 100 patient-years}}$$

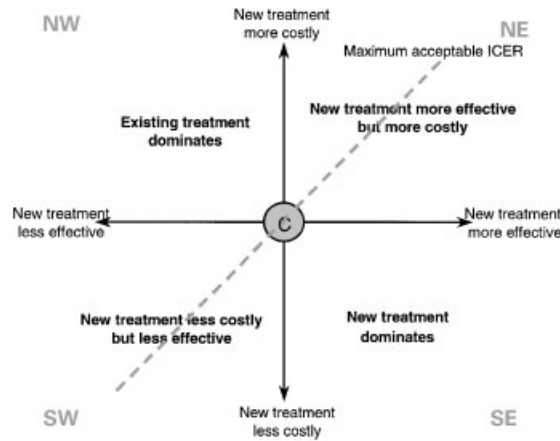


Figure 1.1 The cost-effectiveness (CE) plane¹¹⁸

The net-benefit approach was developed to better manage uncertainty in the economic evaluation of health interventions.^{124,125} The net-benefit framework is a reformulation of the traditional CEA equation, which incorporates λ directly into the equation. The net-benefit equation provides a measure of ‘net-benefit’ and a simple decision rule, which states that an intervention should be implemented only if the ‘net-benefit’ is positive. An important result of this reformulation is the conversion of the traditional CEA’s ratio statistic, the ICER, to the net benefit’s linear statistic.

There are two different formulations of net-benefit, the net-monetary-benefit (NMB)¹²⁵ and the net-health-benefit (NHB).¹²⁴ Both statistics are a direct function of λ . An intervention’s net-monetary-benefit (NMB) is calculated by subtracting the additional cost from the additional effect valued in dollars:

$$NMB = \lambda \bullet \mu_{\Delta E} - \mu_{\Delta C} > 0$$

An intervention’s net-health-benefit (NHB) is calculated by subtracting the additional cost valued in effects from the additional effect:

$$NHB = \mu_{\Delta E} - \frac{\mu_{\Delta C}}{\lambda} > 0$$

Sample analogues are used to estimate mean effect and mean cost differences to provide the estimated net-benefit statistics ($N\hat{M}B$ and $N\hat{H}B$)

$$N\hat{M}B = \lambda \bullet \Delta\bar{E} - \Delta\bar{C}$$

$$N\hat{H}B = \Delta\bar{E} - \frac{\Delta\bar{C}}{\lambda}$$

The net-benefit framework has many advantages compared to the traditional CEA, of which only three primary ones will be discussed, followed by one potential disadvantage. One of the primary advantages is its ability to better manage uncertainty in CEAs. This ability is a result of the more attractive statistical properties associated with its linear form compared to previously discussed statistical problems associated with ICER ratio statistics. In contrast to the traditional CEA's ICER, it is relatively simple to construct parametric confidence intervals to manage uncertainty in a stochastic CEA within the net-benefit framework. Unlike the ICER, variance of net benefits can be directly estimated from sample mean cost and effects. The variance of NMB is determined by:

$$N\hat{M}B = \lambda^2 \text{var}(\Delta\bar{E}) + \text{var}(\Delta\bar{C}) - 2\lambda \text{cov}(\Delta\bar{E}, \Delta\bar{C})$$

and the variance of NHB is determined by:

$$N\hat{H}B = \text{var}(\Delta\bar{E}) + \frac{1}{\lambda^2} \text{var}(\Delta\bar{C}) - \frac{2}{\lambda} \text{cov}(\Delta\bar{E}, \Delta\bar{C})$$

With variance known and help from the central limit theorem ($N\hat{B}$ is asymptotically normal), a $(1-\alpha)\%$ confidence interval can easily be constructed as:

$$NB \pm Z_{\frac{\alpha}{2}} \sqrt{\sigma^2_{NB}}$$

where $N\hat{B}$ is the estimated net-benefit measure with variance σ^2_{NB} and $z_{\alpha/2}$ is the critical value obtained from the standard normal distribution.¹¹⁸ Another primary advantage of the net-benefit framework is that it does not suffer from the interpretation ambiguities associated with the traditional CEA's ICER. An intervention's positive net-benefit is unambiguously favorable.¹²⁴ The last primary advantage of the net-benefit framework, which is due to its linear nature, is that it opens the door to a myriad of econometric techniques that can be employed for economic analysis to include the formulation of the cost-effectiveness problem within a standard regression type framework.¹¹⁸ The net-benefit's many other advantages include additional statistical advantages over the ICER and its relative ease in performing stochastic analyses with multiple comparators.¹²⁴

A potential disadvantage of the net-benefit statistic is that, as discussed, it is a direct function of γ , a value unknown to the analyst in some cases. This potential disadvantage can be addressed by obtaining a range of potential values for γ from the literature and/or expert opinion and applying sensitivity analyses.¹²⁴ Paradoxically, this disadvantage of having to specify the maximum willingness to pay per unit of health gain is related to an additional criticism of the ICER ratio. Namely, the ICER ratio by itself does not, in the case of an intervention in the Southwest and Northeast quadrants of the cost-effectiveness plane, provide sufficient information to health care policy decision makers to adopt a particular treatment intervention.^{118, 124}

The net-benefit regression framework involves the integration of the net-benefit statistic into the standard regression type framework. This integration enables the estimation of cost-effectiveness within a standard type regression framework. Cost-effectiveness is estimated by employing the net-benefit framework to define a net-benefit value for each subject.

$$NMB_i = \lambda \bullet E_i - C_i$$

where E_i and C_i are the observed effect and cost for subject i . An example of a linear model for subject i 's net-monetary-benefit can be expressed as:

$$NMB_i = \alpha + \delta t_i + \varepsilon_i$$

where α is the intercept term, t_i a treatment dummy taking the value zero for the standard treatment and the value of one for the treatment under consideration, and ε is a stochastic error term. The regression coefficient δ on the treatment dummy provides the estimate of the incremental net-benefit (cost-effectiveness). The significance of the net-benefit regression methodology is that additional explanatory variables can be added to the model to directly assess their impact on cost-effectiveness:

$$NMB_i = \alpha + \sum_{j=1}^p \beta_j \chi_{ij} + \delta t_i + \varepsilon_i$$

where there are p covariates χ . In this case, the coefficient δ provides the incremental net-benefit of implementing the new treatment while controlling for confounding variables. In addition, interaction terms can be added to the model:

$$NMB_i = \alpha + \sum_{j=1}^p \beta_j \chi_{ij} + \delta t_i + t_i \sum_{j=1}^p \gamma_j \chi_{ij} + \varepsilon_i$$

where the final summation represents the interaction between the treatment variable and the covariates. The magnitude and significance of the coefficients γ_j on the interaction term indicate how cost-effectiveness of treatment is expected to vary at the margin; large and statistically significant γ_j 's point towards important patient subgroups.¹¹⁸

There are two distinct advantages of the net-benefit regression method, which prompted the selection of this methodology of a CEA for this research. First, the incorporation of the net-benefit statistic into a regression type framework allows for the addition of covariates in the model. This ability enables the researcher to control for heterogeneous groups in observational studies. Second, as discussed, the addition of interaction terms in the net-benefit regression type framework enables the researcher to examine the marginal impact of covariates on incremental cost-effectiveness, thus allowing the identification of important patient subgroups.

For this study, the net-benefit regression method of CEA will be incorporated into a cost-utility analysis (CUA) framework. Therefore, it will be necessary to identify health state values for the effect variable of the net-benefit statistic in addition to a range of conditional λ s.

Health State Values

The majority of pharmacoeconomic studies conducted in the field of osteoporosis research have been cost-utility analyses.^{2, 126} The cost-utility approach has been favored by health economists because it enables them to convert the multiple clinical outcomes of osteoporotic fracture (hip, vertebral, and wrist fracture), each associated with different consequences for morbidity into a single currency, quality-adjusted life-years (QALYs).

The conversion of outcomes to the single currency of QALYs enables comparisons of cost-effectiveness of osteoporosis interventions with other diseases and with established thresholds of cost-effectiveness. The NOF guidelines suggest an osteoporotic fracture intervention is cost-effective if it produces a cost per quality-adjusted life-year (QALY) of \$30,000 a year or less.¹²⁷ A key component of the QALY measure is the health state value (HSV) or utility.

A QALY is the product of the HSV assigned to each state associated with an intervention's outcome multiplied by the length of time spent in each state. A HSV is the weight assigned to a particular health state, ranging from 0 to 1, where a weight of 0 corresponds to a health state judged to be equivalent to death and 1 corresponds to perfect health. In general, the HSV's employed in previous pharmacoeconomic studies for the key health events associated with osteoporosis have been primarily based on expert opinion, rather than from empirical evidence.^{2,126} Yet, sensitivity analyses of these studies have revealed that the cost per QALY estimates are highly sensitive to the HSV values used.¹²⁸ To identify empirically derived HSV estimates for use in this study, a systemic review of published literature reporting empirical estimates of HSVs for key osteoporosis health states was conducted. A total of only six published papers^{66, 129-133} were found to report HSVs for one or more osteoporosis related conditions.

The empirically derived HSV estimates reported in these studies differed significantly from NOF values² obtained from a panel of experts and with each other. The between study differences can be attributed to differences in the derivation of the estimates.¹¹⁶ Two recently published reviews^{116, 134} and the Washington Panel on Cost-

effectiveness¹³⁵ recommend the use of generic preference-classification systems, such as the EQ-5D¹³⁶ and the Health Utility Index (HUI)-III,¹³⁷ as the preferred preference-based health outcome measures for health-policy decision making. Only four¹²⁹⁻¹³² of the six studies reported HSVs obtained from generic preference-classification systems for one of the three osteoporosis health states: hip fracture, vertebral fracture, and wrist fracture. Table 1.6 below identifies the fracture type, study, generic preference classification system, and HSVs obtained in these studies. The HSVs derived by the NOF² are provided for comparison purposes.

Table 1.6 Empirical estimates of HSVs for hip, vertebral, and wrist fractures¹¹⁶

Fracture Type	Study	Preference Classification System	Health State Value (SD)	
Hip	NOF Review ²	NA – Expert panel	1 st year: 0.3817; subsequent years: 0.855	
	Gabriel et al. ¹²⁹	HUI-II	0.68 (0.18)	
Vertebral	Brazier et al. ¹³²	EQ-5D	1 st 6 mo: 0.49 (0.32); 12 mo: 0.48 (0.38)	
	NOF ²	NA – Expert panel	0.97	
	Gabriel et al. ¹²⁹	HUI-II	0.80 (0.16)	
	Oleksik et al. ¹³¹	EQ-5D	# of fractures	HSV
			0	0.82
			1	0.75
			2	0.74
Wrist			3	0.81
			≥ 4	0.66
			Lumbar	0.78
			Thoracic	0.68
	NOF ²	NA – Expert panel	1 st year 0.96; subsequent years 0.98	
	Dolan et al. ¹³⁰	EQ-5D	0.981	

The HSVs for hip fracture obtained by Brazier et al.¹³² were significantly lower than the values obtained by Gabriel et al.¹²⁹ The lower scores can be partially attributed

to Brazier et al.'s use of the time-trade-off technique as opposed to the other study's use of the standard-gamble technique, and the fact that Brazier et al.'s population was significantly older and had lower HSVs at baseline compared to EQ-5D normative values.¹¹⁷ Even though the HSVs differed significantly between the two studies, the proportionate loss between the two studies was similar when comparing Gabriel et al.'s HUI estimate of 0.68 to the age/sex norm found in Canada of 0.82.¹³⁸ The HSVs for vertebral fracture obtained by Gabriel et al.¹²⁹ and Oleksik et al.¹³¹ were similar. Dolan et al.¹³⁰ provide the only empirically derived HSV for wrist fracture.

A current limitation of the generic preference-classification system derived HSVs for osteoporosis related conditions, is the use of these values in specific age groups that were not included in the original studies. In order to extrapolate the HSVs from these studies to specific age groups, Brazier et al.¹¹⁶ proposed the use of a set of reference case HSVs. This proposal is based upon the assumption of a constant proportional effect of fractures on HSVs, and assumes that the better the health status, the more the individual has to lose. Brazier et al.¹¹⁶ developed a set of reference case HSVs, based on generic preference-classification system derived HSVs, to be used as multipliers of age-specific HSV population norms to estimate the proportionate effect of fracture on HSVs in the first year. In the development of the set of reference case HSVs, Brazier et al.¹¹⁶ favored the incorporation of HSVs derived from the EQ-5D over HUI-II because the EQ-5D is available on more osteoporosis related conditions than the HUI-II. The reference case values recommended by Brazier et al.¹¹⁶ are provided in Table 1.7 below. The reference

case HSVs are the multipliers for the proportionate effect of fracture on HSVs in the first year.

Table 1.7 Reference case HSVs to be applied to population norms¹¹⁶

Health State	Value	Source
Hip Fracture	0.797 (95% CI, 0.651-1.1012)	Brazier et al. ¹³²
Vertebral Fracture	0.909 (95% CI, 0.84-0.97)	Oleksik et al. ¹³¹
Wrist Fracture	0.981 (95% CI, 0.978-0.986)	Dolan et al. ¹³⁰

The reference case values set forth by Brazier et al.¹¹⁶ for use as multipliers for the proportionate effect of fracture on HSVs were adopted for use in a recent osteoporosis cost-utility analysis performed by Kanis et al.⁸⁵ In this study, Kanis et al.⁸⁵ applied the reference case values to population norms derived by Kind et al.¹¹⁷ (see Table 1.8 below). The population norms derived by Kind et al.¹¹⁷ were obtained from the administration of the EQ-5D to over 3,000 representative members of the UK general population. The use of population norms derived by Kind et al.¹¹⁷ were ideal for this cost-utility analysis, since the population of interest for both studies was the same.

Table 1.8 Normative HSVs derived from the administration of EQ-5D to UK general population¹¹⁷

Age	HSV
45-49	0.840
50-54	0.850
55-59	0.802
60-64	0.829
65-69	0.806
70-74	0.747
75-79	0.731
80-85	0.699
85+	0.676

Two potential problems arise in the application of Brazier et al.'s¹¹⁶ set of reference case HSVs. First, is the extension of health state valuations for subsequent years. Second, is a possible lack of population normative data for the study population of interest. As previously discussed, the set of reference case values developed by Brazier et al.¹¹⁶ are to be applied to the first year of the fracture event. Brazier et al.¹¹⁶ did not provide a set of reference case HSVs for subsequent years, but instead suggested the development of a set of guesstimates, which allow for some degree of recovery.

The other potential problem with the application of the set of reference case HSVs set forth by Brazier et al.¹¹⁶ is a lack of population normative data for the study population of interest. For example, there is not any EQ-5D or other generic preference-classification system normative data for the U.S. population. However, this concern may be minimal. Johnson et al.¹³⁹ determined “that differences in health-state valuations are unlikely to have important implications when using EQ-5D population norms derived for one population to be used in another, in the absence of population-specific normative data.”

Maximum Acceptable Willingness to Pay (λ)

Stinnett and Mulholland¹²⁴ recommend conducting a net-benefit analysis for a range of values for λ and to report estimated net-benefit as a function of λ . In 1998, the NOF² established \$30,000 per QALY gained as an acceptable threshold for cost-effectiveness. Since that time, several studies^{114, 140-142} have used \$30,000 as a threshold for cost-effectiveness. Therefore, a range of values centered-around the \$30,000 threshold for cost-effectiveness would be reasonable.

STATINS AND FRACTURE RISK

Introduction

Statins, a class of drugs used in the management of hypercholesterolemia, may be of value in the management of osteoporotic fractures. Statins have been shown to have a mechanism of action similar to aminobisphosphonates, a class of drugs used in the management of osteoporosis. Aminobisphosphonates supposedly exert their anti-osteoporosis effect by inhibiting the farnesyl diphosphonate enzyme in the mevalonate pathway, which leads to osteoclast apoptosis, thus resulting in decreased bone resorption.^{143, 144} Statins exert their lipid lowering effect through the mevalonate pathway also, by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase. Thus, it is believed that statins may also act as inhibitors of osteoclast formation. Moreover, the possible anti-osteoporosis effect of statins has been supported by the finding that some statins also stimulate bone formation.

Mundy et al.¹⁴⁵ first discovered the bone forming potential of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors in December of 1999, during their search for anabolic agents that enhanced osteoblast differentiation and bone formation. In their research, Mundy et al. employed a screening technique to isolate compounds that activated the promoter of the bone morphogenetic protein-2 (BMP-2) gene, which is known to enhance osteoblast differentiation and bone formation. After screening over 30,000 compounds, the investigators discovered that members of the statin drug class (lovastatin, fluvastatin, simvastatin, and mevastatin) activated the promoter of the BMP-2 gene. Mundy et al. conducted two in vivo experiments in rats to

assess the osteoblast differentiation and bone formation potential of statins. In the first experiment, lovastatin and simvastatin were injected into subcutaneous tissue overlying murine calvaria and demonstrated a 50% increase in new bone formation after only 5 days of treatment. In the second experiment, the statins were orally administered to ovariectomized as well as rats with intact ovaries, which resulted in increased trabecular bone volume of the femur and lumbar vertebrae between 39% and 94% after 35 days of treatment. Although Mundy et al. observed a decrease in the number of osteoclasts, they believed this effect was minimal compared to the effect on bone formation and osteoblast maturation. As a result of these studies suggesting the biologic plausibility of a statin effect on bone, a number of epidemiological studies have been conducted to assess the association of statin use with bone density and fracture incidence.

Epidemiological Studies

A systematic literature review of published epidemiological studies exploring the association between statin use with bone density and fracture incidence was conducted. In all, eight studies were identified, five case-control studies,¹⁴⁶⁻¹⁵⁰ one retrospective chart review,¹⁵¹ one prospective study,¹⁵² and one secondary analysis of RCT data.¹⁵³ In addition, a meta-analysis¹⁵⁴ examining the use of statins and fractures has recently been published. The results from these observational studies are inconsistent. Five^{146-148, 150, 151} of the eight studies provided evidence of an association between statin use and reduced risk of fracture. In contrast, three of the studies^{149, 152, 153} provide no evidence of an association. To even further muddy the evidence pool, two case-control studies,^{147, 149} conducted on the same data base, reached opposite conclusions. The overall results of a

meta-analysis¹⁵² suggest that there is an association between statin use and reduced risk of fracture. The remainder of this section provides an overview of the eight observational studies. One of the first published observational studies was conducted by Chung et al.

Chung et al.¹⁵¹ conducted a retrospective chart-review study to assess the effect of statins on BMD in 69 Korean patients with Type II diabetes mellitus. Statin users (n = 36) were matched (age, sex, body weight, postmenopausal status, and fasting blood glucose levels) with controls (n = 33). Both treatment group patients and controls were excluded if they had any disease related to bone mineral metabolism or were taking any medication that affected bone mineral metabolism. Exposure to the study statins (lovastatin, pravastatin, and simvastatin) was obtained via chart review. The outcome, BMD of the lumbar spine, femoral trochanter, Ward's triangle, femoral neck, and total hip, were measured at baseline and at follow-up, with a mean follow-up time for the exposure group of 15 months (± 3 months) and for the control group of 12 months (± 2 months). In addition to the matching employed, potential confounders controlled for included age and body mass index (BMI). Both univariate and multiple regression statistics were employed in the analysis.

At follow-up, men in the control group (n = 15) did not experience a significant change in BMD from baseline, whereas women experienced a significant decrease in BMD of the spine ($p < 0.05$). In contrast, all statin users experienced a significant increase in BMD of the femoral neck ($p < 0.001$). Males statin users (n = 14) experienced a significant increase in BMD of both the femoral neck ($p < 0.05$) and femoral trochanter ($p < 0.05$), whereas female statin users (n = 22) only experienced a

significant increase in BMD of the femoral neck ($p < 0.05$). The percentage of statin users with a 2% or more increase in BMD of the spine and total hip was 30.6%, whereas the percentages for the control group was 15.6% and 9.1%, respectively. The percentage of male statin users who experienced a 2% increase in BMD of the spine and total hip was greater than the percentage of women. The investigators attributed the gender-related differences to the fact that bone loss in males is primarily secondary to a physiological decrease in osteoblastic function, whereas bone loss in postmenopausal women is due more from increased bone resorption. The results of this study are limited for primarily two reasons: 1) the retrospective clinical record review design, and 2) the extremely small sample size. Another possible limitation of the study was the use of subjects with type-II diabetes mellitus, who may have altered bone mineral metabolism.

Three large case-control studies,¹⁴⁶⁻¹⁴⁸ all published within a week of each other, followed the clinical study by Chung et al.,¹⁵¹ which today provide the best evidence supporting an association between statin use and decreased risk of fractures. Chan et al.¹⁴⁶ conducted a population based, case-control study using pharmacy and claims data obtained from six health-maintenance organizations (HMOs) located in different regions of the U.S. to determine the relationship between statin use and fracture risk among older women. Data were collected on women ≥ 60 years of age who were members of one of the selected six HMOs between October 1994 and September 1997. Patients who met inclusion criteria and had a hospital or outpatient diagnosis code for non-pathological fracture of the hip, humerus, distal tibia, vertebrae, or wrist between October 1996 and September 1997 and had no diagnosis code for any of these fracture sites between

October 1994 and September 1996 (cases; n = 928) were matched (age and HMO) with controls (n = 2,747) who did not sustain such fractures. Both cases and controls were excluded if they had a diagnosis code for major trauma, cancer of the bone, breast, colon, or lung, multiple myeloma, metastatic cancer, or pathological fracture. They were also excluded if they received a prescription for hormone replacement therapy, bisphosphonates, calcitonin, anticonvulsant drugs, or thyroid hormones. Exposure to statins and other antilipidemic agents was determined from automated pharmacy claims for the two-year period prior to the fracture date. The number of statin dispensings was used as a surrogate measure for cumulative statin exposure. In addition to the matching, additional potential confounders controlled for by restriction and regression modeling included concomitant medications (antipsychotics, long-acting hypnotics, antidepressants, thiazide diuretics, hypoglycemic agents, and corticosteroids) and the number of hospital admissions during the 12 months preceding the fracture date. Logistic regression models were used to develop adjusted odds-ratios (ORs) to assess the association between statin use and fracture risk.

Study results revealed a significant reduction in the risk of fracture in women with ≥ 13 dispensings of statins (exposure approximately equal to one year) in the two-year period prior the fracture date (OR, 0.48; 95% CI, 0.27 to 0.83). The group of patients who received < 13 dispensings of a statin or who received other antilipidemic agents did not show a significant reduction in the risk of fractures. Although this study controlled for a number of potential confounders, potential confounders not controlled for included: body mass index (BMI), smoking, and physical activity. Other limitations of the study

were that it excluded women taking medications known to treat osteoporosis and no BMD measurements were obtained.

Meier et al.¹⁴⁷ conducted a large population based, nested case-control analysis using the UK-based General Practice Research Database (GPRD) to determine whether use of statins or other antilipidemic medications were associated with a reduced risk of fractures. Within the GPRD, a base population of 91,611 patients, ages 50-89, stratified into three separate groups: group 1 - patients with at least one prior prescription for an antilipidemic agent (n = 28,340); group 2 - patients with a hyperlipidemic diagnosis but no antilipidemic agent (n = 13,271); and group 3 - patients without a hyperlipidemic diagnosis or treatment (n = 50,000), was followed from the start of follow-up until the person developed a fracture, left the practice, or died. Start of follow-up was defined as the date of the first prescription for any antilipidemic agent for group one or the date exactly one year after computer recording of prescriptions began for groups two and three. Patients who sustained a fracture (cases; n = 3,940) were matched (age, sex, general practice visited, calendar time, years of GPRD history prior to index date) with controls (n = 23,379) who did not sustain a fracture. Both cases and controls were excluded if they had a diagnosis of osteoporosis, osteomalacia, cancer, or alcoholism or had a previous prescription for bisphosphonates. The degree of exposure to a statin was determined by exposure timing and duration of use. Patients were categorized according to exposure timing into one of three categories based on last statin prescription received prior to index date: current use (< 30 days), recent use (30-89 days), and past use (> than 90 days). Patients were also categorized according to exposure duration by number of

statin prescriptions into one of four categories: 1-4, 5-9, 10-19, and > 20. In addition to the matching employed, potential confounders controlled for included: medications affecting fracture risk (corticosteroid use, hormone replacement therapy), smoking status, BMI, and number of general practice visits prior to index date. Logistic regression models were used to develop adjusted ORs to assess the association between statin use and fracture risk.

The results of this study demonstrated that current statin use was associated with a significant reduction in the risk of all fractures (OR, 0.55; 95% CI, 0.44 to 0.69; $p < 0.001$). This association was present after only one to four months of treatment. Current use of other antilipidemic agents was not associated with a significant fracture risk reduction. One of the limitations of this study was that it did not control for level of physical activity and diet as potential confounders. In addition, this study also excluded women with a diagnosis of osteoporosis and no BMD measurements were obtained.

Wang et al.¹⁴⁸ conducted a similar case-control analysis using the New Jersey Medicare, Medicaid, and Pharmacy Assistance for the Aged and Disabled Program data to determine whether the use of statins was associated with reduced hip fracture risk in a population of 6,110 New Jersey residents ≥ 65 years of age. Patients who sustained a hip fracture during 1994 (cases; $n = 1,222$) were matched (age and gender) with controls ($n = 4,888$) to determine the risk of hip fracture in the 180 days or three-years prior to surgery for hip fracture (index date). Both cases and controls were required to have no evidence of previous hip fracture prior to their index date. The degree of exposure to statins was determined by exposure and quantity of use. Exposure to statins was

determined by the presence of at least one prescription for a statin 180 days and 3 years prior to index date. Patients were also categorized into quartiles based on calculated medication possession ratios (MPRs) for the 180 days prior and three years prior to index date. In addition to the matching criteria employed, potential confounders controlled for included race, insurance status, medications known to effect fracture risk (hormone replacement therapy, oral corticosteroids, thiazide diuretics, psychoactive agents), medications known as markers for specific clinical conditions, medical conditions (ischemic heart disease, congestive heart failure, hypertension, diabetes, and cancer), a modified Charlson comorbidity index, and extent of health care utilization. Logistic regression models were used to develop adjusted ORs to assess the association between statin exposure and hip fracture risk.

Study results revealed that use of a statin was associated with a significant reduction in the risk of hip fracture 180 days and three-years prior (OR, 0.50; 95% CI, 0.33 to 0.76) and (OR, 0.43; 95% CI, 0.40 to 0.82), respectively. In addition to the overall results, this study provided three pieces of evidence that the relationship between statin use and fracture risk may be both causal and related to the biological activity of statins. First, in contrast to use of statins, current use of other antilipidemic agents was not associated with a risk reduction in fracture – same indication as statins but different mechanism of action. Second, this study demonstrated a clear use-response relationship for both short-term and longer-term use. The short-term use-response relationship established in this study further supports the findings of Meier et al.¹⁴⁷ who demonstrated the benefits of statin therapy after short-term use. Third, current use of statins was

associated with the greatest reduction in risk (OR, 0.29; 95% CI, 0.10 to 0.81), even after adjusting for total extent of statin use. Although this study controlled for a plethora of potential confounders, investigators noted that all potential confounders may not have been controlled for. Other limitations of this study included the lack of BMD measurements and diagnosis of osteoporosis.

A more recent study providing evidence of a relationship between statins and a reduced risk of fracture was conducted by Pasco et al.,¹⁵⁰ who performed a cross-sectional case-control study using data from the Geelong Osteoporosis Study to determine whether statins decrease the risk of fracture and whether there is an association between statin use and BMD. Data were analyzed for the period February 1994 through February 1996. Patients who were ≥ 50 years of age and with non-pathological incident fractures (n = 573) were matched (age) to women without incident fractures (n = 802). Exposure, current use of, and duration of statin use information was obtained from self-reported questionnaires along with information on other medications, lifestyle, diet, calcium intake, alcohol consumption, smoking, and exercise. The fracture outcomes were identified from radiological reports and BMD of the femoral neck, lumbar spine, anterior-posterior projection, and total body was measured at baseline and follow-up. Potential confounders addressed for fracture associated with statin use included BMD, age, weight, dietary calcium, alcohol use, smoking (current and ever), activity levels, and exposure to hormone replacement therapy, corticosteroids, and calcium and/or vitamin D supplements. Potential confounders addressed for BMD changes associated with statin

use included age, weight, and fracture/non-fracture status. Univariate and multivariate statistics were used to assess the risk of fracture and changes in BMD among statin users.

There were fewer statin users in the fracture group (16) compared to the non-fracture group (53). The results revealed a significant reduction in fracture risk (OR, 0.45; 95% CI, 0.25 to 0.80) and a 3% greater adjusted BMD at the femoral neck ($p = 0.08$). Although there was an increase in BMD among statin users, the reduction in fracture risk was not completely explained by the increase in BMD. A limitation of this study was the small number of statin users, which limited the power to detect changes in BMD.

In contrast to the five observational studies providing evidence of a relationship between statin use and decreased the risk of fracture and increased BMD, three studies provide evidence of no relationship. Reid et al.¹⁵³ conducted a secondary analysis on data from an RCT on the effect of statin use on mortality due to coronary heart disease, the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study. In this study, 9,014 patients with ischemic heart disease were randomly assigned to either pravastatin 40mg/day or placebo and followed for a mean of six years. Reid et al. obtained the frequency of fracture from adverse-event reports.

A total of 183 patients in the placebo group sustained a fracture compared with 175 in the pravastatin group. The results revealed no significant reduction in the risk of fracture in overall rates of fracture (HR, 0.94; 95% CI, 0.77 to 1.116), in women only (HR, 0.80; 95% CI, 0.55 to 1.18), nor in patients older than 65 years of age (HR, 0.93; 95%CI, 0.68 to 1.27). There are two major limitations with this study. First, the study

population was at low risk of fracture. Patients were not recruited on the basis of fracture history or low bone density, and only 17% of the population was women. The second limitation, and probably the most significant, was this study assessed the risk of fracture only with pravastatin. In vitro studies suggest that pravastatin has virtually no effect on the BMP-2 promoter gene, which is thought to be responsible for statin's osteoblastic effect.¹⁵⁵

Van Staa et al.¹⁴⁹ performed a population-based case-control study using the UK-based GPRD, the same database used by Meier et al., to determine the risk of fracture among statin users. Data were analyzed from 1987 to July 1999. Patients who were ≥ 50 years of age and with a diagnosis code for a fracture of the vertebrae, clavicle, humerus, radius/ulna, carpus, hip, ankle, or foot during their enrollment (cases; $n = 81,880$) were matched (age, gender, and medical practice visited) with an equal number of controls of fracture. Exposure to statins was determined by reviewing patients' prescription history prior to fracture date. Patients were categorized as either current users (statin prescription within 6 months of fracture date), past users (statin users who stopped therapy 6 months prior fracture date), or non-users. A similar method was used to assess exposure to other non-statin antilipidemic medications. The daily dose of statin was obtained from written instructions for the last statin prescription prior to the fracture date. In addition to the matching employed, potential confounders addressed included smoking and BMI when known, medications associated with fracture risk (anticonvulsants, non-steroidal anti-inflammatory drugs, methotrexate, hormone replacement therapy, thiazide diuretics, anxiolytics/hypnotics, antipsychotics, anti-depressants, anti-Parkinson drugs, systemic

and inhaled corticosteroids, and bronchodilators), and clinical conditions associated with fracture risk (diabetes mellitus, rheumatoid arthritis, hyperthyroidism, congestive heart failure, seizures, anemia, dementia, depression, psychotic disorders, cerebrovascular accident, and chronic obstructive pulmonary disease). Conditional logistic regression models were used to estimate adjusted odds ratios (ORs).

The results revealed no reduction in fracture risk among current statin users (OR, 1.01; 95% CI, 0.88 to 1.16), past statin users (OR, 1.01; 95%CI, 0.78 to 1.32), among long-term (> 12 months) statin users (OR, 1.17; 95%CI, 0.99 – 1.40), among short-term users (OR, 0.71; 95% CI, 0.50 to 1.01), or in users of statins at higher doses compared to those at lower doses. The results of this study contradict the findings of Meier et al.¹⁴⁷ There are several potential explanations for the difference in findings. First, statin users may have been monitored more closely than non-statin users, thus increasing the probability of a reported fracture (measurement bias). Second, exposure to statins increased substantially over time. Lastly, no information on medication adherence was collected (compliance bias).

LaCroix et al.¹⁵² conducted a prospective cohort study of the Women's Health Initiative (WHI) Observational Study group. A total of 93,716 postmenopausal women, aged 50 to 79, were enrolled in the observational group from 1994 to 1998. Investigators followed the group for the occurrence of clinical fractures of any type and a subset of the group (n = 6,442) for changes in BMD of the total hip, anterior-posterior spine, and total body. The follow-up time ranged from two to six years with a median duration of 3.9 years. Hip fractures were confirmed by centralized review of radiology reports whereas

all other fractures were self-reported. Fractures were classified into three mutually exclusive categories: hip fractures, lower arm or wrist fractures, and other clinical fractures. Exposure to statins was categorized into three categories by duration (< 1 year, 1 to 3 years, or > 3 years) and by demonstrated lipid-lowering potency (low, medium, or high). Potential confounders controlled for included medications associated with risk of fracture (thiazide diuretics, alendronate, corticosteroids, hypnotics, and hormone replacement therapy), clinical conditions (history of fracture, coronary heart disease), dietary supplements, calcium and/or vitamin D, race/ethnicity, current and past smoking, coffee consumption, alcohol consumption, activity level, physical function, and BMI. Multivariate Cox proportional hazards survival models were employed in the statistical analysis.

The results of the study revealed no reduction in the risk of fracture or increase in BMD among statin users. The multivariate-adjusted rates hazard ratios for current statin use were 1.22 (95% CI, 0.83 to 1.81) for hip fracture, 1.04 (95% CI, 0.85 to 1.27) for lower arm or wrist fracture, and 1.11 (95% CI, 1.00 to 1.22). This study shared a limitation of the study conducted by Reid et al.¹⁵³ Approximately 23% of statin users (1.9% of the 8.4% statin users) were taking pravastatin. Other study limitations included: information on dose was not recorded, low use of statins long-term, and did not account for statins taken in the past which were no longer being taken at base-line.

Bauer et al.¹⁵⁴ performed a series of meta-analyses to determine the effect of statin use on BMD and fracture rates. The first meta-analysis examined four prospective studies: the Study of Osteoporotic Fractures (SOF), the Fracture Intervention Trial (FIT),

the Heart and Estrogen/Progestin Replacement Study (HERS), and the Rotterdam Study, all of which had baseline measurements of medication use, BMD, other health related information, and subsequent fracture outcomes. The results of this meta-analysis revealed that after adjustment for age, BMI, physical activity or physical disability, smoking, health status, and use of estrogen and bisphosphonates, BMD was significantly higher among statin users in the HERS study but not in the other three studies and that there was a trend (not statistically significant after adjustment) towards lower risk of new hip and nonspine fractures among statin users.¹⁵⁴

In the second meta-analysis, the investigators combined the data from the four prospective studies with four previously reported observational studies. The results of this meta-analysis revealed a reduced risk of hip fracture (summary OR, 0.43; 95% CI, 0.25 to 0.75) and non-spine fractures (summary OR, 0.69; 95% CI, 0.75 to 0.88). The summary results obtained were robust when the meta-analysis was restricted to studies with adjusted results, prospective cohort studies, or were limited to women.¹⁵⁴

The final meta-analysis was conducted on combined data from two placebo-controlled clinical trials with cardiovascular endpoints: the Lipid study (Long-term Intervention with Pravastatin in Ischemic Disease) and the 4S Study (Scandinavian Simvastatin Survival Study), which captured self-reported fractures. This meta-analysis failed to demonstrate a reduced risk of hip fracture (summary OR, 0.87; 95% CI, 0.48 to 1.58) or nonspine fracture (summary OR, 1.02; 95%CI, 0.83 to 1.26). The failure to show a significant risk reduction of fracture was not surprising, considering the meta-analysis included the Lipid Study (pravastatin).

Results from the recent epidemiologic research, regarding the association between fracture risk and the use of statins, are inconsistent. Current evidence suggests that either more observational studies or better yet large, randomized, controlled, prospective studies need to be conducted to establish the certainty of the reported association between statins and fracture risk. Given the unknown association between statin use and fracture risk, statin use should be considered for inclusion as a confounding variable in any study assessing the effectiveness of an intervention in preventing osteoporotic fractures.

RETROSPECTIVE DATABASE STUDIES IN OUTCOMES RESEARCH

In a world of limited resources and health care budgets, health care decision-makers are increasingly relying on information obtained from retrospective database studies, in addition to that provided by RCTs, to make more informed decisions about the cost and effectiveness of medical treatments. Although retrospective database studies provide a wealth of “real-world” information, both researchers and decision-makers need to be conscious of the limitations and methodological challenges of this type of research. This section provides an overview of some of the design and interpretation issues associated with retrospective database studies. The first part of this overview is based on an article by Motheral et al.,¹⁵⁶ which discusses the advantages, limitations, and methodological challenges of retrospective database studies, particularly in regards to validity. The second part of the overview, provides a checklist for retrospective database studies, produced by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force,¹⁵⁷ that was developed to assist decision-makers in evaluating the quality of retrospective database studies.

Although RCTs represent the gold standard for research, the methodological approach employed in RCTs often limits generalizability of study findings. The methodological approaches which limit generalizability include: the inclusion/exclusion criteria used in patient selection methods, which result in a non-representative subset of the population; treatment settings and measurement approaches that limit generalizability to routine clinical settings; and the short follow-up period of most RCTs, which limits their ability to address issues of long-term cost-effectiveness. An additional limitation is the expense involved in conducting an RCT. In contrast, retrospective database research allows researchers to examine “real world” medical care utilization, in large study populations for longer observation periods, thus allowing for examination of specific subpopulations. Moreover, compared to RCTs, retrospective database studies provide decision-makers with a relatively inexpensive and quick approach to answering the time-sensitive questions.

Some of the methodological challenges encountered in retrospective database studies can potentially impact the internal, construct, and external validity of study results. Internal validity concerns making appropriate inferences about the relationship between a study’s dependent and independent variables. Motheral et al.¹⁵⁶ identified the following potential threats to internal validity: the *Diagnostic Information* coding system (e.g., the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)), influenced by incentive and reimbursement systems, provider behavior, and/or documentation systems, may lead to under- and over-coding, thus making coding unreliable or invalid; failure to take *Compliance* with treatment interventions into account

may lead to misinterpretation of relationship between treatment intervention and outcome variable; *Exposure Misclassification* may reduce the likelihood detecting a significant difference (when one actually exists) when the misclassification is random or may introduce bias if misclassification is systematically related to exposure-outcome relationship; *Referral Bias* may distort the exposure-outcome relationship when patient referral is influenced by drug exposure status; *Protopathic Bias* confuses the relationship between cause and effect and occurs “if a particular maneuver was started, stopped, or otherwise changed because of the baseline manifestation caused by a disease or other outcome event...”;¹⁵⁸ finally, *Confounding* by other risk factors may distort a true effect or relationship when present.

Construct validity refers to “the degree to which a variable accurately reflects the phenomenon that it purports to measure.”¹⁵⁶ Motheral et al.¹⁵⁶ identified several examples of construct validity problems. The common source of the construct validity problems in the examples provided was the operational definition used to define a variable. For instance, in one example the operational definition used to define a diagnosis was not jointly exhaustive and mutually exclusive, and thus led to the incorrect categorization of patients with the disease of interest.

External validity is the “validity with which we can infer that the presumed causal relationship can be generalized to and across alternate measures of the cause and effect and across different types of persons, settings, and times.”¹⁵⁹ Even though retrospective database studies are less likely than RCTs to have external validity problems, there are a number of issues in retrospective database studies which may limit generalizability.

Regarding threats to external validity, Motheral et al.¹⁵⁶ made the following points: *Characteristics of the Study Population* such as demographics, insurance coverage, and rate of disease or injury need to be considered before making generalizations to other populations; health *Plan Design* characteristics such as copays, formularies, and access to providers and *Regional Practice Patterns* can influence cost and utilization, and therefore may limit generalizability of findings to other populations with different health plan designs; finally, *Cost Differences* exist across place and time and thus may limit generalizability.

Other important considerations for health care decision-makers interpreting retrospective database studies were outline in a recent ISPOR publication. The ISPOR Task Force on Retrospective Databases published a “Checklist for Retrospective Database Studies.”¹⁵⁷ The checklist, consisting of 27 questions, was developed to assist decision makers in the evaluation of a published retrospective database study’s quality; however, the checklist is also of value to investigators designing such a study. The checklist (Table 1.9) focuses on three areas of the retrospective database study: the database, the methodology, and the conclusions.

Table 1.9 Checklist for retrospective database studies¹⁵⁷

<p>Database</p> <p>Q1) Relevance: Have the data attributes been described in sufficient detail for decision makers to determine whether there was a good rationale for using the data source, the data source's overall generalizability, and how the findings can be interpreted in the context of their own organization?</p> <p>Q2) Reliability and Validity: Have the reliability and validity of the data been described, including any data quality checks and data cleaning procedures?</p> <p>Q3) Linkages: Have the necessary linkages among data sources and/or different care sites been carried out appropriately, taking into account differences in coding and reporting across sources?</p> <p>Q4) Eligibility: Have the authors described the type of data used to determine member eligibility?</p> <p>Methods</p> <p>Q5) Data analysis plan: was a data analysis plan, including study hypotheses, developed a priori?</p> <p>Q6) Design selection: Has the investigator provided a rationale for a particular research design?</p> <p>Q7) Research design limitations: Did the author identify and address potential limitations of that design?</p> <p>Q8) Treatment effect: For studies that are trying to make inferences about the effects of an intervention, does the study include a comparison group and have the authors described the process for identifying the comparison group and the characteristics of the comparison group as they relate to the intervention group?</p> <p>Q9) Sample selection: Have the inclusion and exclusion criteria and the steps used to derive the final sample from the initial population been described?</p> <p>Q10) Eligibility: Are the subjects eligible for the time period over which measurement is occurring?</p> <p>Q11) Censoring: Were inclusion/exclusion or eligibility criteria used to address censoring and was the impact on study findings discussed?</p> <p>Q12) Operational definitions: Are case (subjects) and end point (outcomes) criteria explicitly defined using diagnosis, drug markers, procedure codes, and/or other criteria?</p> <p>Q13) Definition validity: Have the authors provided a rationale and/or supporting literature for the definitions and criteria used and were sensitivity analyses performed for definitions or criteria that are controversial, uncertain, or novel?</p> <p>Q14) Timing of outcome: Is there a clear temporal relationship between the exposure and outcome?</p> <p>Q15) Event capture: Are the data, as collected, able to identify the intervention and outcomes if they actually occurred.</p> <p>Q16) Disease history: Is there a link between the natural history of the disease being studied and the time period for analysis?</p>

Table 1.9 Checklist for retrospective database studies (cont'd)¹⁵⁷

Methods (continued)

Q17) Resource validation: For studies that examine costs, have the authors defined and measured an exhaustive list of resources affected by the intervention given the perspective of the study and have resource prices been adjusted to yield consistent valuation that reflects the opportunity cost of the resources?

Q18) Control variables: If the goal of the study is to examine treatment effects, what methods have been used to control for other variables that may affect the outcome of interest?

Q19) Statistical model: Have the authors explained the rationale for the model/statistical method used?

Q20) Influential cases: Have the authors examined the sensitivity of the results to influential cases?

Q21) Relevant variables: Have the authors identified all variables hypothesized to influence the outcome of interest and included all available variables in their model?

Q22) Testing statistical assumptions: Do the authors investigate the validity of the statistical assumptions underlying their analysis?

Q23) Multiple tests: If analyses of multiple groups are carried out, are the statistical tests adjusted to reflect this?

Q24) Model prediction: If the authors utilize multivariate statistical techniques in their analysis, do they discuss how well the model predicts what it is intended to predict?

Discussion/Conclusion

Q25) Theoretical Basis: Have the authors provided a theory for the findings and have they ruled out other plausible alternative explanations for findings?

Q26) Practical versus statistical significance: Have statistical findings been interpreted in terms of their clinical or economic relevance?

Q27) Generalizability: Have the authors discussed the populations and settings to which the results can be generalized?

STUDY RATIONALE AND OBJECTIVES

Osteoporosis poses an increasingly substantial clinical, economic, and health-related quality-of-life (HRQOL) burden to the individual, the U.S. health care system, and society in general, as the U.S. population continues to age. In response, the pharmaceutical industry continues to introduce new medications to meet the growing demand for effective osteoporosis treatment interventions, which has and continues to increase costs for the treatment and prevention of osteoporosis. Given the growing clinical and economic burden of the disease and faced with the dilemma of making formulary decisions about new treatment interventions, there is an increasing demand among health care policy decision-makers for economic evaluations of the new interventions being introduced into the market and for their own current osteoporosis intervention strategies.

To date, the majority of published osteoporosis pharmacoeconomic studies employ some method of economic modeling, typically Markov modeling, to evaluate the prospective, long-term cost-effectiveness of various osteoporosis interventions. The purpose of these economic evaluations is to serve as a guide to efficient long-term resource allocation for healthcare policy decision-makers. While these types of economic evaluations are important, especially for organizations contemplating initiation of a new resource intensive intervention, retrospective economic evaluations also provide valuable information to health care policy decision-makers about the impact of previous decisions and cost-effectiveness of current osteoporosis prevention and treatment strategies.

In January 2000, the TRICARE Management Activity (TMA) and the Department of Defense (DoD) Pharmacy Board of Directors determined that funds allocated to military treatment facility (MTF) pharmacies through Program Budget Decision (PBD) No. 041 should be used to increase and standardize the availability of drugs at MTF pharmacies. In response, the DoD Pharmacoeconomic Center (PEC) developed a set of recommended changes and additions to the DoD Basic Core Formulary (BCF) for the DoD Pharmacy and Therapeutics (P&T) Committee to consider. The BCF is a list of medications that are required to be on all MTF formularies. On 26 January 2000, the DoD P&T committee added alendronate, along with seven other medications, to the BCF.¹⁶⁰ Since the addition of alendronate to the BCF, alendronate utilization has increased exponentially, with annual expenditures exceeding \$61 million. Alendronate accounts for approximately 58% of the DoD's 6th highest expenditure drug class, bone resorption inhibitors. To date, no formal health economic evaluation of alendronate or other current osteoporosis interventions has been performed to determine the costs and effects of current osteoporosis treatment interventions employed by the DoD.¹⁶¹

The goal of this study is to evaluate the economic, clinical and humanistic outcomes of current osteoporosis interventions employed in the prevention of osteoporotic fractures in the Department of Defense population. The perspective taken in this health economic evaluation is that of the DoD PEC. The results of this study will provide the DoD PEC with valuable information regarding the incidence of osteoporotic fracture in the DoD population, the clinical effectiveness of current treatment interventions, and both the aggregate and marginal cost-effectiveness of current treatment

interventions. Armed with this information, the PEC will be able to make more informed decisions about how to best optimize the economic, clinical, and humanistic outcomes of osteoporosis treatment interventions in a health system with limited resources and health care budgets.

Epidemiology of Osteoporotic Fracture in the DoD Population

Objective 1

Determine the cumulative incidence and relative risk of osteoporotic fractures and by fracture type for the cohort as a whole and stratified by intervention group - Osteoporosis Diagnosis/Alendronate (ODA), Osteoporosis Diagnosis/HRT (ODHRT), Osteoporosis Diagnosis/AHRT (ODAHRT) (combination of alendronate and HRT), Osteoporosis Diagnosis/No Treatment (ODNOTX), and No Osteoporosis Diagnosis/No Treatment (NOODTX) and by risk factors (age, osteoporosis diagnosis, oral corticosteroid use, previous fracture history, and < 80% compliance) and statin use during the observation period.

Effectiveness of Treatment Interventions

Objective 2

Determine the odds ratio for osteoporotic fracture and by fracture type for each active intervention group (ODA, ODHRT, ODAHRT) versus ODNOTX and compare the between group differences in relative risk.

Objective 3

Determine the significance of risk factors (age, fracture history, oral corticosteroid use, and < 80% compliance) and statin use, for the prediction of osteoporotic fracture, while controlling for intervention group.

Objective 4

Compare the time to fracture for the treatment groups. There are two general goals of this objective: 1) to describe the proportion of cases free of a fracture event at various points in time, and 2) to assess the relationship between survival time and the set of covariates (risk factors [age, fracture history, corticosteroid use, and < 80% compliance] and statin use) to determine whether treatment differences are present after statistically controlling for the other covariates.

Economic and Humanistic Outcomes Analysis***Objective 5***

To determine the incremental cost-effectiveness of treatment interventions, using the net-benefit regression method of CEA.

Objective 6

Explore the importance of covariates on the marginal cost-effectiveness of an intervention, thus identifying important patient subgroups.

HYPOTHESES

The following section lists the null hypotheses for those objectives that involve comparison of groups (Objectives 2 and 4)

Objective 2

- **H_{O(1)}** The odds ratio (OR) of osteoporotic fracture for intervention group ODA = ODHRT = ODAHRT = ODNOTX = 1.
- **H_{O(2)}** The odds ratio (OR) of osteoporotic hip fracture for intervention group ODA = ODHRT = ODAHRT = ODNOTX = 1.
- **H_{O(3)}** The odds ratio (OR) of osteoporotic vertebral fracture for intervention group ODA = ODHRT = ODAHRT = ODNOTX = 1.
- **H_{O(4)}** The odds ratio (OR) of osteoporotic wrist fracture for intervention group ODA = ODHRT = ODAHRT = ODNOTX = 1.

Objective 4

- **H_{O(5)}** There is no difference in the proportion of cases free of a osteoporotic fracture event at various points in time between the four intervention groups (ODA, ODHRT, ODAHRT, ODNOTX).
- **H_{O(6)}** There is no difference in the proportion of cases free of a osteoporotic hip fracture event at various points in time between the four intervention groups (ODA, ODHRT, ODAHRT, ODNOTX).
- **H_{O(7)}** There is no difference in the proportion of cases free of a osteoporotic vertebral fracture event at various points in time between the four intervention groups (ODA, ODHRT, ODAHRT, ODNOTX).

- **H_{O(8)}** There is no difference in the proportion of cases free of a osteoporotic wrist fracture event at various points in time between the four intervention groups (ODA, ODHRT, ODAHRT, ODNOTX).
- **H_{O(9)}** There is no difference between treatments (ODA, ODHRT, ODAHRT, ODNOTX) in time to osteoporotic fracture after statistically controlling for other covariates (risk factors and statin use).
- **H_{O(10)}** There is no difference between treatments (ODA, ODHRT, ODAHRT, ODNOTX) in time to osteoporotic hip fracture after statistically controlling for other covariates (risk factors and statin use).
- **H_{O(11)}** There is no difference between treatments (ODA, ODHRT, ODAHRT, ODNOTX) in time to osteoporotic vertebral fracture after statistically controlling for other covariates (risk factors and statin use).
- **H_{O(12)}** There is no difference between treatments (ODA, ODHRT, ODAHRT, ODNOTX) in time to osteoporotic wrist fracture after statistically controlling for other covariates (risk factors and statin use).

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Chapter 2

Methodology

This chapter presents a discussion of the study's institutional review board approval, data sources, time frame, population, design, data collection process, and the data analysis for each of the study's objectives. The discussion of the study's design is presented in the context of the net-benefit regression method of cost-effectiveness analysis (CEA) framework, the method of CEA selected for this study.

INSTITUTIONAL REVIEW BOARD (IRB) APPROVAL

This study was reviewed by The University of Texas Institutional Review Board (IRB) as well as the Brooks City Base IRB. Approval was granted from both institutions on 16 February 2004 and 11 February 2004, respectively.

DATA SOURCES

Data for this study were obtained from the Department of Defense (DoD) Pharmacoeconomic Center (PEC), located at Ft Sam Houston, Texas. The PEC is a tri-service (Air Force, Army, Navy) organization whose mission is to improve the clinical, economic, and humanistic outcomes of drug therapy in support of the readiness and managed healthcare missions of the Military Healthcare System (MHS).

Three different databases were used in this study: the Uniformed Services Prescription Database (USPD), the Pharmacy Data Transaction Service (PDTs), and the Military Health Service (MHS) Management and Analysis Reporting Tool (M2). The USPD, PDTs, and M2 databases capture demographic and health care information on

active duty military members, retirees and their family members who are enrolled in TRICARE, the military health care plan. DoD beneficiaries have the option of selecting from three different TRICARE health care plans which provide varying levels of access to both military and civilian medical facilities and pharmacies. All beneficiaries have access to military treatment facility (MTF) pharmacies, regardless of TRICARE health plan option selected.

The USPD database is a centralized repository of all MTF prescription transactions since October 1998. MTFs upload their prescription transactions to the USPD database on a weekly basis. The USPD database includes the customary prescription information fields along with other demographic information fields (see Table 2.1 for a list data fields obtained from the database for this study). The USPD database was used to collect part of the prescription data used in this study (01 October 1998 through 30 June 2001). The primary limitation of the USPD database is that it does not capture prescription transactions which occur outside the MTF. Although all beneficiaries can obtain prescriptions from an MTF pharmacy at no cost, some elect to their obtain prescriptions through TRICARE retail network pharmacies (TRNP) and/or the TRICARE mail order pharmacy (TMOP) for an additional copay. During fiscal year 2003, 20.4% of the 6,187,185 beneficiaries who used their pharmacy benefit, obtained their prescriptions solely from TRNP and an additional 1.4% through TMOP.¹ Therefore, to ensure a more comprehensive representation of a patient's prescription transaction history, prescription utilization data was also obtained from PDTs.

The Pharmacy Data Transactions Service (PDTS) tracks all prescriptions filled at MTFs, the TRNP, and the TMOP. Unfortunately, the PDTS database only includes prescription information as of 23 June 2001, the date that the database was deemed to be fully operational. For this study, data from PDTS was collected from 01 July 2001 through 30 September 2003 (see Table 2.1 for a list data fields obtained from the database for this study).

The M2 database is a centralized database maintained by the DoD Health Affairs Executive Information/Decision Support (EI/DS) Program Office. The M2 database is a centralized repository of all ambulatory care and hospitalization health care transactions across military healthcare services. It includes demographic, enrollment data, diagnostic and procedural codes and other claims data from both MTF and commercial network facilities. For the purposes of this study, the M2 database was used to identify diagnostic and procedure codes (see Table 2.1 for a list data fields obtained from the database for this study).

Table 2.1 Summary of data fields by database source for this study

Source Database	Data Field
M2	Cost (Price Raw, Amount Paid Raw)
	Service Date
	Primary and Secondary Diagnosis
	Primary Procedure
USPD	Brand Name
	Generic Name
	Dosage Form
	Strength
	Pharmacy Identifier
	Rx Number
	Rx Status (New or Refill)
	Date Dispensed
	Quantity Dispensed
	Days Supply
	Fill Number
	Refills Allowed
	Refills Remaining
PDTS	NDC
	Brand Name
	Generic Name
	Strength
	Dosage Form
	Date Dispensed
	Quantity Dispensed
	Days Supply
	Rx Status (New or Refill)
	Fill Number
	Rx Number
	Service Category (Retail Network, Mail Order, MTF)
	Total Submitted Amount Due

STUDY TIME FRAME

The final data set used in this study consisted of diagnostic and prescription data from 1 October 1998 through 30 September 2003, fiscal years (FY) 1999 through 2003 (the DoD fiscal year begins 1 October and ends 30 September).

STUDY POPULATION

The target population for this study was female TRICARE beneficiaries aged 50 and older. However, the PEC does not have access to a comprehensive database that identifies all eligible TRICARE beneficiaries. In place of such a database, the PEC uses transaction records from the USPD database and/or the PDTS database as a proxy to define the population of enrolled TRICARE beneficiaries. Therefore, the accessible study population was restricted to patients for whom there was a record of at least one MTF prescription filled during the FY99 to FY00 period (1 October 1998 through 30 September 2000) in the USPD database. In other words, female TRICARE beneficiaries aged 50 and older who did not have at least one prescription filled during the FY99 to FY00 period were ineligible for inclusion in the study. The general criteria used to determine inclusion of patients' records from the accessible population were: female gender, age ≥ 50 , and continuous TRICARE enrollment from FY99 to FY03. The decision to use age ≥ 50 was based on the age criteria used in previous pharmacoeconomic studies. Healthcare claims data from the M2 database were used as a proxy to define continuous enrollment in TRICARE. Patients who had at least one claim during the assessment period (FY99 to FY00) and at least one claim in FY01, FY02, and FY03 were defined as being continuously enrolled during the study.

STUDY DESIGN

A sample-based retrospective cohort study was performed to evaluate the clinical, economic, and humanistic outcomes of osteoporotic fractures in the DoD population. Cohort studies are observational studies which identify subsets of a defined population

and follow them over time, looking for differences in outcome. In a retrospective cohort study, all relevant events (both exposures and outcomes of interest) have already occurred when the study is initiated. In this study, patient subsets were defined by exposure to treatment intervention. Five intervention groups were selected for observation: Osteoporosis Diagnosis/Alendronate (ODA), Osteoporosis Diagnosis/HRT (ODHRT), Osteoporosis Diagnosis/AHRT (ODAHRT) (combination of alendronate and HRT), Osteoporosis Diagnosis/No Treatment (ODNOTX), and No Osteoporosis Diagnosis/No Treatment (NOODTX). The outcomes of interest were osteoporotic fractures, specifically osteoporotic fractures of the hip, vertebrae, and wrist. Along with the exposure and outcomes variables of interest, this study also examined the impact of the following risk factors for osteoporotic fracture that were identifiable through the administrative and prescription databases: age, fracture history, oral corticosteroid use, and intervention compliance. The statin drug class was included as a possible confounding variable, given the recent reports in the literature of an association between statin use and osteoporotic fracture.

The five-year sample based retrospective cohort study was subdivided into two periods, an assessment period (FY99 to FY00) and an observation period (FY00 to FY03). During the assessment period, intervention groups were identified by exposure to intervention. The ODA group included all patients who received their first alendronate prescription during FY00, which is subsequently referred to as the index-prescription and the date on which it was filled as the index-date. An additional inclusion criterion applied to this group was that they did not receive HRT in FY99 or FY00. The

ODAHRT group consisted of patients who were first prescribed alendronate during FY00 and who received and continued to receive HRT at least 90 days after their first alendronate prescription. Since alendronate is almost exclusively used to treat osteoporosis, with the exception of Paget's disease, all alendronate patients were considered to have a diagnosis of osteoporosis. The ODHRT group included all patients who were first prescribed HRT during FY00 and had an existing diagnosis of osteoporosis. The ODNOTX group consisted of all patients who had an existing diagnosis of osteoporosis and who were not taking either alendronate or HRT during the assessment period. The NOODTX group consisted of a sample of patients without an existing diagnosis of osteoporosis and who were not taking either alendronate or HRT. An additional exclusion criterion applied to all intervention groups was prior or current use of other osteoporosis medications, with the exception of calcium or vitamin D. In addition to a diagnosis of osteoporosis, exposure to other risk factors and covariates (age, fracture history, oral corticosteroid use, and statin) use was identified during the assessment period.

During the three-year observation period, each patient was followed for the occurrence of osteoporotic fractures. In addition, continued or new exposure to corticosteroids and statins was also determined. The three-year observation period for the active intervention groups ODA, ODAHRT, and ODHRT started with the first index-prescription in FY00 (rolling enrollment), whereas the observation period for ODNOTX and NOODTX started at the beginning of FY00. Figure 2.1 below provides a diagram of the study design.

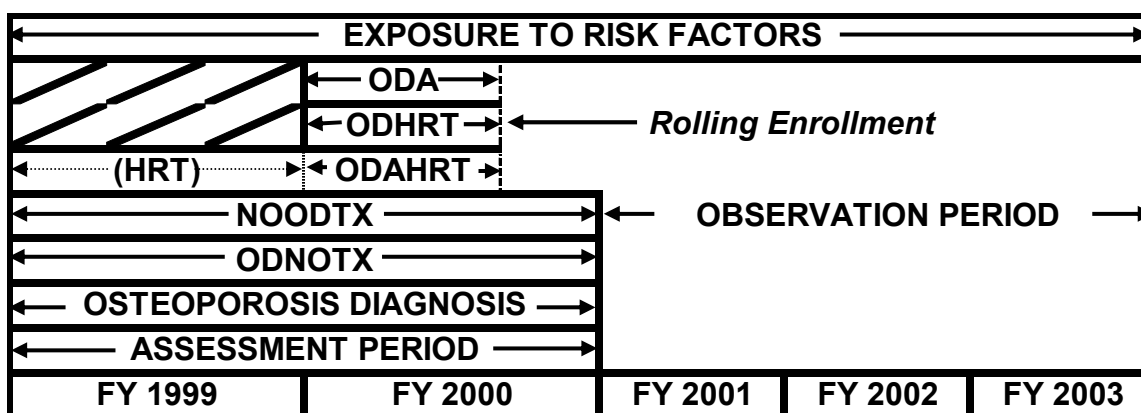


Figure 2.1 Study Design Diagram

Using this study design, epidemiologic analyses were performed to determine the incidence and relative risk of osteoporotic fractures in the DoD population, the significance of risk factors for osteoporotic fracture that are identifiable from administrative and prescription claims databases, and the time to osteoporotic fracture event. Finally, a net-benefit regression method of cost-effectiveness analysis was employed to assess the overall cost-effectiveness of alendronate, HRT, and AHRT, and to explore the importance of covariates on the marginal cost-effectiveness of the interventions, thus identifying important patient subgroups.

All analyses were performed from both an intent-to-treat (ITT) and non intent-to-treat (Non-ITT) study design. For the intent-to-treat study design, exposure to treatment intervention was measured at the onset of the observation period. In the non intent-to-treat design, exposure was measured throughout the observation period. Patients who deviated from index-intervention during observation period were removed from the analysis. The net-benefit regression method of CEA serves as a logical framework to further describe the methodology employed in this study.

NET-BENEFIT REGRESSION COST-EFFECTIVENESS ANALYSIS METHOD

As previously discussed, in this methodology a net-monetary-benefit statistic:

$$NMB_i = \lambda \bullet E_i - C_i$$

where E_i and C_i are the observed effect and cost for subject i and λ is the maximum willingness to pay per unit of health gain, is incorporated into a standard regression framework

$$NMB_i = \alpha + \sum_{j=1}^p \beta_j \chi_{ij} + \delta t_i + \sum_{j=1}^p \gamma_j (t_i * \chi_{ij}) + \varepsilon_i$$

where α is the intercept term, the first summation represents the p covariates χ , t is a treatment dummy taking on the value zero for the standard treatment and the value of one for the treatment under consideration, δ is the regression coefficient on the treatment dummy, the final summation represents the interaction between the treatment variable and the covariates, and ε is a stochastic error term. The two primary advantages of the net-benefit regression method of CEA are derived from the equation above. First, additional explanatory variables can be added to the model to directly assess their impact on cost-effectiveness. The regression coefficient δ provides the estimate of the incremental net-benefit (cost-effectiveness) while controlling for confounding variables. Second, the addition of interaction terms to the regression model provides an estimate of the impact of covariates on the marginal cost effectiveness, hence the ability to identify important patient subgroups. The magnitude and significance of the coefficients γ_j on the interaction term indicate how the cost-effectiveness of treatment is expected to vary at the margin; large and statistically significant γ_j 's point towards important patient subgroups.

The following sub-section describes how the variables will be obtained for the net-benefit regression equation.

Net-Monetary-Benefit Statistic Variables ($NMB_i = \lambda \bullet E_i - C_i$)

Maximum Acceptable Willingness to Pay (λ) - As recommended by Stinnett and Mullhay,² this NMB analysis was conducted for a range of values for λ and the estimated NMB was reported as a function of λ . A range from \$0 to \$100,000 per QALY for λ was used. This range was selected because it included the National Osteoporosis Foundation's (NOF)³ established acceptable threshold for cost-effectiveness of \$30,000 per QALY and provided an upper sensitivity limit over three times that of the cost-effectiveness threshold.

Effect (E_i) – As previously discussed, a cost-utility analysis (CUA) was selected as the approach for health economic evaluation in this study. This approach enables the multiple clinical outcomes of osteoporotic fracture (hip, vertebral, and wrist fracture), each with different consequences for morbidity, to be converted into a single currency, quality-adjusted life-years (QALYs). Therefore, it was necessary to convert the effect variable (fracture outcomes), obtained from the M2 database, from a binary variable (fracture, no fracture) to a continuous QALY variable. A QALY is the product of the health state value (HSV) assigned to each state associated with an intervention's outcome multiplied by the length of time spent in each state. A HSV is the weight assigned to a particular health state, ranging from 0 to 1, where a weight of 0 corresponds to a health state judged to be equivalent to death and 1 corresponds to perfect health. The HSVs used in this study to estimate QALYs were calculated by the application of a set of reference

case HSV multipliers, described by Brazier et al.,⁴ to a set of age-adjusted population norms, defined by Kind et al.⁵ Refer to Tables 1.7 & 1.8 for the set of reference case values and age-adjusted population norms, respectively.

Using the set of reference case values and age-adjusted population norms, a QALY was calculated for each individual patient for the assessment period (baseline) and each year of observation. Since the observation period was subdivided into year units, each year's QALY was equivalent to the HSV(s) assigned that year. The HSV assigned to a particular patient was dependent upon: the presence of and type of fracture event; previous fracture events, since some fractures impact the quality-of-life beyond the event-year; and age of patient. For patients who sustained a fracture, the subsequent years' HSVs were adjusted by half to account for some degree of recovery. The change in QALY scores from baseline for each observation year was summed across the three years of observation to yield a total change in QALY score. An example of the calculation of QALYs is provided below in Table 2.2.

Table 2.2 Calculation of QALYs example

*Mrs. Smith, a 65 year old woman, sustained a hip fracture in year two and a vertebral fracture in year three.			
Year of Observation	Reference Case Value	Age-adjusted Population Norm	QALY
First	1 (no event)	0.806	0.806
Second	0.797(hip fracture)	0.806	0.642
Third	0.899 (hip fracture, subsequent year) – (1- 0.909 [vertebral fracture]) = 0.808	<u>0.806</u>	<u>0.651</u>
Total Change in Three-Year QALY Score Due to Fractures		2.418	-2.099 = 0.319

The operational definition used to identify osteoporotic fracture events from the M2 database is a modification of the operational definition employed by Westfall et al.⁶ The operational definition used for this study uses the same four criteria employed by Westfall et al.⁶ but adds an additional fifth inclusion criterion. The first four criteria used by Westfall et al.⁶ and in this study used both ICD-9 diagnosis and procedure codes and CPT-4 procedure codes to identify fracture by type. A claim was considered to be an osteoporotic fracture if it met one of the following criteria:

- The primary diagnosis is a pathological fracture (ICD-9 codes 733.1-733.19);
- The primary diagnosis is a fracture of a specific site of the vertebrae (805.00-805.9; 806.0-806.91), wrist (813.0-813.93; 814.0-814.19), or hip (820-821.39) or there is a CPT-4 procedure code for fracture of the vertebrae (22305-22328), wrist (25600-25624), or hip (27193-27248; 27500-27514) or there is an ICD-9 procedure code for fracture of the vertebrae (0353), wrist (7902-7992; 7842), or hip (7925-7995; 7845) and the secondary diagnosis is a pathological fracture;
- The primary diagnosis is osteoporosis (ICD-9 codes 733.0-733.09) and the secondary diagnosis was a specific site fracture or there was a CPT-4 or ICD-9 procedure code for fracture; or
- The secondary diagnosis is osteoporosis (ICD-9 codes 733.0-733.09) and the primary diagnosis was a specific site fracture or there was a CPT-4 or ICD-9 procedure code for fracture

The additional fifth criterion used in this study was:

- Patients in intervention groups ODA, ODAHRT, ODHRT, and ODNOTX by definition have an existing diagnosis. Therefore, any patient with a primary diagnosis of fracture of the hip, vertebrae, or wrist was assumed to have an osteoporotic fracture, although a secondary diagnosis of a pathological fracture or osteoporosis was not present.

Westfall et al.⁶ employed a series of criteria, based on CPT-4 procedure codes, to distinguish a new osteoporotic fracture claim from an existing osteoporotic fracture claim. Unfortunately, the same criteria employed by Westfall et al.⁶ could not be used in this study, primarily as a result of poor MTF procedure coding. A total of 2,767 out of 33,512 claims meeting the operational definition of fracture did not include a primary procedure code. As a result, this study employed a single criterion to distinguish a new osteoporotic fracture claim from an existing osteoporotic claim:

- A claim was considered a new osteoporotic fracture episode if it was the first claim for a subject following a 6-month period with no osteoporotic fracture claims for the same specific fracture site.

Westfall et al.⁶ also used a 6-month interval as one of the criteria for determining a new osteoporotic fracture event.

Costs (Ci) – Only direct medical costs, cost of medication and fracture treatment costs, were included in the analysis. The medication treatment cost reflects the final cost to the MHS from each point of service. For medication treatment costs, if a prescription was dispensed from an MTF, the cost is the acquisition cost of the medication. If a prescription was dispensed from either the National Mail Order Pharmacy or TRICARE

Retail Network Pharmacy, the cost reflects the “Total Submitted Amount Due” to the MHS from the managed care contractor. Since the USPD database did not contain any type of medication cost field, medication costs were determined by multiplying the sum total units (tablets, capsules, transdermal systems) dispensed for each medication by its FY03 average weighted unit cost, which was obtained from the PDTS database. The average weighted unit cost was calculated from the average cost incurred at each point of service (MTF, Mail Order, and Retail Network) weighted by their percentage of all transactions.

Fracture treatment costs were obtained from the M2 database. In the M2 database, the MHS reports several different types of costs, dependent upon the point of service and method used to calculate cost. Two different costs were used in this study to determine fracture treatment costs, “Price Raw” and “Amount Paid Raw.” If the MTF is the point of service, the cost reported is “Price Raw.” In general, “Price Raw” reflects the worldwide average full cost across all MTFs for a particular type of care. If the point of service is the managed care network, the cost reported is “Amount Paid Raw” which is the amount paid by the MHS to the managed care network provider for a particular claim. All fracture treatment costs were compounded by a 5% interest rate to FY03 costs.

Covariates – (χ_j)

In the net-benefit regression methodology, the inclusion of covariates in the regression model enables the researcher to control for the presence of confounding variables. This ability is especially significant in an observational study given the potential heterogeneous nature of the intervention groups. The osteoporosis net-benefit

regression model employed in this research included covariates that were known risk factors for osteoporotic fracture, could be readily obtained and allowed discrete categorization using an administrative claims or prescription database, and were previously found to be either statistically significant or were recommended for future economic studies. The following risk factors met the inclusion criteria and were operationalized using claims markers in the administrative claims or prescription databases: age, osteoporosis diagnosis, history of previous osteoporotic fracture, corticosteroid use, statin use, and intervention compliance.

Age – The age of the patient was the age of the patient at the start of the observation period (01 October 1999). This information was obtained from the M2 database.

Previous Osteoporotic Fracture – Patients with a previous osteoporotic fracture were identified during the risk assessment period, FY99 to FY00, using the same operational definition employed for the effect variable (E_i). This information was also obtained from the M2 database.

Corticosteroid Use - Two variables were created to assess the oral corticosteroid-induced risk of osteoporotic fracture, dose and duration. Patients were categorized according to the weighted average daily dose of prednisone or prednisone dosage equivalents into one of four categories ($\leq 5\text{mg}$, $> 5\text{mg} \leq 10\text{mg}$, $> 10 \leq 20\text{mg}$, and $> 20\text{mg}$) (see Table 2.3 for prednisone strengths and dosage equivalents used as claims markers for steroid use). Each subject was also categorized according to duration of use into one of three categories (≤ 180 days, > 180 days ≤ 365 days, > 365 days). The

duration of use variable is defined as total days of therapy during the study period (continuous or not). These two variables were then used to form 12 dose-duration categorical variables, one for each possible combination of dose and duration. The drug, dose, and days supply information was obtained from the USPD and PDTs databases.

Table 2.3 Prednisone strengths and dosage equivalents⁶

Generic Name	Strength	Prednisone Equivalent
Betamethasone	0.6mg	5mg
Cortisone acetate	25mg	5mg
Dexamethasone	0.75mg	5mg
Dexamethasone	1mg	6.7mg
Dexamethasone	1.5mg	10mg
Dexamethasone	2mg	13.3mg
Dexamethasone	4mg	26.7mg
Dexamethasone	6mg	40mg
Hydrocortisone	20mg	5mg
Methylprednisolone	4mg	5mg
Methylprednisolone	8mg	10mg
Methylprednisolone	16mg	20mg
Methylprednisolone	24mg	30mg
Methylprednisolone	32mg	40mg
Prednisolone	5mg	5mg
Prednisone	5mg	5mg
Prednisone	10mg	10mg
Prednisone	20mg	20mg
Prednisone	50mg	50mg
Triamcinolone	4mg	5mg

Intervention Compliance - The compliance with each intervention was measured by determining the medication possession ratio (MPR). The MPR definition employed in this study was the same definition used by Okano et al.⁷ in a previous study utilizing the USPD database. The MPR was defined for each patient as the supply of medication dispensed, measured in days, divided by the number of days in a 36-month study period.

Since this study was performed on an intent-to-treat basis, any purposely discontinued treatment was not accounted for in the MPR.

Statin Use – Statin use was included as a potential confounding variable. Like corticosteroid use, two variables were used to assess the statin-induced risk of osteoporotic fracture, dose and duration. Patients were categorized according to the weighted average daily dose of statin into one of two categories, low-dose or high-dose therapy, based upon percent reduction in low density lipoprotein cholesterol (LDL-C) (see Table 2.4). Patients receiving statin medication doses capable of achieving a 35% reduction or more in LDL-C were considered to be on high-dose therapy. More specifically, high-dose and low-dose therapy was defined as follows: high-dose = doses of simvastatin $\geq 40\text{mg}$, doses of atorvastatin $\geq 20\text{mg}$, doses of cerivastatin $> 0.4\text{mg}$, doses of fluvastatin $> 80\text{mg}$, and doses of lovastatin $\geq 80\text{mg}$. All other statin doses were considered to be low-dose therapy. Each subject was also categorized according to duration of statin exposure into one of three categories (\leq one-year, $>$ one-year \leq two years, $>$ two-years). The duration of exposure variable is defined as total days of therapy during the study period (continuous or not). As with the corticosteroid variables, these two variables were then used to form six dose-duration categorical variables, one for each possible combination of dose and duration. The drug, dose, and days supply information was obtained from the USPD and PDTS databases. Patients who received pravastatin were not included, since earlier in vitro studies suggest that pravastatin has virtually no effect on the BMP-2 promoter gene, which is thought to be responsible for statin's osteoblastic effect.

Table 2.4 Statin dose equivalency chart⁸

% LDL-C Reduction	HMG-CoA Reductase Inhibitor					
	Pravastatin	Fluvastatin	Cerivastatin	Lovastatin	Simvastatin	Atorvastatin
18	10mg	20mg	0.2mg	10mg	5mg	10mg
19						
20						
21	20mg	40mg		20mg	10mg	
22						
23						
24						
25						
26						
27	40mg	80mg	0.3mg	40mg	20mg	
28						
29						
30				0.4mg	80mg	40mg
31						
32						
33						
34						
35					0.8mg	80mg
36						
37						
38						
39						
40						
41					80mg	
42						
43						
44						
45						
46						
47						
48						
49						
50						
51						
52						
53						
54						
55						
56						
57						
58						

Interventions (δt_i)

As previously noted, five intervention groups were identified during the risk assessment period and were followed during the three-year observation period: Osteoporosis Diagnosis/Alendronate (ODA), Osteoporosis Diagnosis/HRT (ODHRT), Osteoporosis Diagnosis/AHRT (ODAHRT) (combination of alendronate and HRT), Osteoporosis Diagnosis/No Treatment (ODNOTX), and No Osteoporosis Diagnosis/No Treatment (NOODTX). However, only four of the intervention groups were included in the net-benefit regression CEA: ODA, ODHRT, ODAHRT, and ODNOTX, with the ODNOTX group serving as a control for the active treatment groups.

Operational definitions were constructed to define the intervention groups. The intervention groups for active treatment were limited to women who first started the treatment in FY00 to avoid any potential for confounding due to duration of treatment intervention. In other words, women who were currently taking the medication prior to the beginning of the observation period were excluded from the intervention groups. The operational definitions used to form the intervention groups from the study population are as follows:

- ODA – Women who filled an alendronate prescription FY00, but who did not have a prescription for alendronate in FY99. Any patient who was prescribed alendronate was assumed to have a diagnosis of osteoporosis;
- ODHRT – Women who filled an HRT prescription FY00, but who did not have a prescription for HRT in FY99. Since HRT can be prescribed for conditions other than osteoporosis, these patients were also required to have a diagnosis of osteoporosis in either FY99 or FY00;

- ODAHRT – Women who filled an alendronate prescription FY00, but who did not have a prescription for alendronate in FY99 and who were currently taking HRT and continued to take HRT at least 90 days after their index alendronate prescription;
- ODNOTX - Women with a diagnosis of osteoporosis in either FY99 or FY00, who did not have a prescription for any osteoporosis treatment with the exception of calcium and/or vitamin D in FY99 or FY00; and
- NOODTX – Women without a diagnosis of osteoporosis and any type of osteoporosis treatment, except for calcium and vitamin D, were identified from a random sample of women ≥ 50 years of age (as of 1 October 1999), who filled any prescription in FY 1999 or FY 2000.

Gender and prescription history were obtained from the USPD database, whereas age, continuous enrollment information, ICD-9 diagnosis and procedure codes, and CPT-4 codes were obtained from the M2 database.

Interaction Terms ($t_i \chi_{ij}$)

Interaction terms between each specific covariate found to be significant and each intervention were formed to estimate the marginal effect of a particular covariate on the intervention while statistically controlling for the presence of other covariates.

DATA COLLECTION PROCESS

A data analyst at the PEC extracted the data from the three databases, patient matched the data via a unique identifier, and then presented the data for this study in a de-

identified format. The following protocol was used to extract the data from the study population to form the study sample.

- Step 1 - Identified women with an osteoporosis diagnosis (ICD-9 Codes 733.0 to 733.09) during the risk assessment period FY99 through FY00. From this population, two of the four intervention groups were identified, ODHRT and ODNOTX.
- Step 2 - ODHRT - Identified women, who filled an HRT prescription in FY00, who did not have a prescription for HRT in FY99.
- Step 3 - ODNOTX - Identified women who did not have a prescription for any osteoporosis treatment with the exception of calcium and/or vitamin D in FY99 and FY00.
- Step 4 - ODA - Identified women who filled an alendronate prescription in FY00, who did not have a prescription for alendronate in FY99. From this population another intervention group was identified, ODAHRT.
- Step 5 – ODAHRT - Identified women who filled an HRT prescription in FY99 and/or FY00, and who had a prescription for alendronate in FY00 but not in FY99.
- Step 6 - NOODTX – Identified via random sampling method using the last digit of the SSN a group of women without a diagnosis of osteoporosis and any osteoporosis related treatment in FY 1999 and FY 2000.

DATA ANALYSIS

All data manipulation and analyses were performed using SAS version 8.02-software. The *a priori* level of significance (alpha) was set at 0.05. The following section is a description of the data analysis procedures for each study objective.

Epidemiology of Osteoporotic Fractures in the Accessible DoD Population

Objective 1

The cumulative incidence of osteoporotic fracture and the cumulative incidence of osteoporotic fracture by type was determined for the cohort as a whole and stratified by intervention group and risk factors during the observation period. The frequency of new osteoporotic fractures was identified from the M2 database employing the previously described operational definition of a new osteoporotic fracture. The cumulative incidence of new osteoporotic fractures during the observation period for the cohort as a whole was defined as:

New cases of osteoporotic fracture occurring during the observation period
All susceptible people present in the sample at the beginning of the observation period

The cumulative incidence of new osteoporotic fractures during the observation period for each intervention group and risk factor was defined as:

New cases of osteoporotic fracture occurring during the observation
period stratified by treatment group or risk factor
All susceptible people present in the sample at the beginning of the observation
period stratified by treatment group or risk factor

In addition, the relative risk of any type of osteoporotic fracture and for each specific type of fracture was determined for intervention groups ODA, ODAHRT, and ODHRT by dividing the cumulative incidence of osteoporotic fracture for those specific intervention

groups by the cumulative incidence for the reference intervention group ODNOTX. The relative risk of any type of osteoporotic fracture and for each specific type of fracture was also determined for the various risk factors by dividing cumulative incidence of osteoporotic fracture in the risk factor exposed group by cumulative incidence of osteoporotic fracture in the non-exposed group.

Effectiveness of Treatment Interventions

Objectives 2 & 3

A series of analyses were performed to determine the relative risk of osteoporotic fractures and the relative risk by type of fracture (hip, vertebral, and wrist) for each treatment group and the significance of risk factors and statin use (confounding variable) in the prediction of osteoporotic fracture events for the cohort. A logistic regression model was used to perform the analyses. This form of regression analysis was selected because it allows one to predict a discrete outcome (fracture, no fracture) from a mix of discrete, dichotomous, and continuous variables. The analyses were performed using the SAS LOGISTIC procedure.

To determine the relative risk of osteoporotic fractures and the relative risk by type of fracture for each intervention group and assess the statistical significance of risk factors and statin use in the prediction of osteoporotic fracture events, a logistic regression model was created. In this model, the dependent variable was a dichotomous variable, which represented whether a patient sustained any type of osteoporotic fracture event. Any patient who sustained one or more osteoporotic fractures was coded as 1 for each fracture occurrence whereas any patient who did not sustain any type of

osteoporotic fracture was coded as 0. The independent variables included the following risk factors and statin use. The patient's age was treated as a categorical variable; history of previous osteoporotic fracture was treated as a dichotomous variable (1 = yes, 0 = no); corticosteroid use, and statin use were treated as categorical variables; and intervention compliance, as determined by the MPR was treated as a dichotomous variable (compliance = 1 (MPR of $\geq 80\%$), 0 = non-compliant).

Objective 4

A series of survival analyses were performed to compare the time to fracture for the treatment groups. There were two general goals of these analyses: 1) to describe the proportion of cases free of a fracture event at various points in time; and 2) to assess the relationship between survival time and a set of covariates (risk factors, and statin use) to determine whether treatment differences are present after statistically controlling for the other covariates.

The Kaplan-Meier method of life tables was used to describe the proportion of cases free of a fracture event at various points in time. The dependent variable, days, was the number of days a case was free of a fracture event during the three-year observation period. Fracture event was the censoring variable that indicated whether a case is fracture free at the end of the observation period. Life tables and survival plots were created for each treatment group for time to first fracture, first hip fracture, first vertebral fracture, and first wrist fracture. The SAS LIFETEST procedure was used to perform the statistical analyses.

A direct Cox proportional-hazards model was used to assess the relationship between survival time and the set of covariates to determine whether treatment differences are present after statistically controlling for the other covariates. In the direct Cox proportional-hazards model, all covariates enter the equation simultaneously and each is assessed as if it entered last. Therefore, each covariate was evaluated as to what it adds to the prediction of survival time that is different from the prediction afforded by all the other covariates. The primary purpose of this analysis was to determine if there was a difference in time to fracture between the treatment groups after adjusting for the effects of the covariates. SAS PHREG was used to perform the Cox proportional-hazards model. As with the Kaplan-Meier method, the dependent variable, days, was the number of days a case was free of a fracture event during the three-year observation period. Fracture event was the censoring variable that indicated whether a case was fracture-free at the end of the observation period.

Economic and Humanistic Outcomes Analysis

Objective 5

The net-benefit regression method of CEA was employed to determine the cost-effectiveness of the DoD's osteoporosis treatment interventions. Four intervention groups were examined: Osteoporosis Diagnosis/Alendronate (ODA), Osteoporosis Diagnosis/HRT (ODHRT), Osteoporosis Diagnosis/AHRT (ODAHRT), and Osteoporosis Diagnosis/No treatment (ODNOTX). The direct treatment costs across the three year observation period were examined from the perspective of the DoD. The

number and type of osteoporotic fracture events were selected as the main effectiveness measure, and were subsequently converted to QALYs as previously described.

The NBR approach was employed to estimate the cost-effectiveness of the intervention groups by estimating:

$$NMB_i = \alpha + \beta_1 age + \beta_2 prevfrac + \beta_3 steroid + \beta_4 statin + \beta_5 compliance + \delta ODA + \delta ODHRT + \delta ODAHRT + \varepsilon_i$$

Net monetary benefits were calculated employing λ values of \$ 0, \$15,000, \$30,000, \$60,000, and \$100,000. SAS REG was used to perform the net-benefit regression.

Objective 6

To examine the impact of covariates on the estimate of the intervention's incremental net-benefit, a model was employed that interacts the treatment dummy with covariates which were found to have a statistically significant increased risk of osteoporotic fracture.

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Chapter 3

Results

This chapter reports the results of the study including frequency distributions and descriptive statistics of the study population and data analysis for objectives one through six. For each objective, two separate analyses are reported, one using an intent-to-treat (ITT) study design and another using a non intent-to-treat (Non-ITT) study design. The non intent-to-treat analysis excluded patients from the cohort who deviated from their index-treatment regimens during the observation period.

After application of the general study and intervention criteria, a total of 49,851 patients were included in the study. The study sample consisted of 4,645 patients in the ODA intervention group, 4,391 patients in the ODAHRT intervention group, 1,620 patients in the ODHRT intervention group, 7,568 patients in the ODNOTX intervention group, and 31,627 patients in the NOODTX intervention group.

INTENT-TO-TREAT VERSUS NON INTENT-TO-TREAT

During the observation period, patients were monitored for deviations from their respective index-treatment regimens. Deviations from index-treatment regimens were identified for each patient via a retrospective review of the patient's prescription history. A deviation from the index-treatment regimen was identified by the dispensing of any other osteoporosis agent during the observation period, other than the index-treatment. A total of 11,568 patients deviated from their respective index-treatment regimen during the observation period, with more deviations occurring in the ODNOTX (43.01%) and ODHRT intervention groups (34.94%) compared to the NOODTX (20.09%), ODA

(17.22%) and ODAHRT (13.53%) intervention groups. Table 3.1 shows the total number of patients in each cohort and the percent decrease in patients for each intervention group from the intent-to-treat (ITT) analysis to the non intent-to-treat (Non-ITT) analysis.

Table 3.1 Frequency distribution and percent decrease from the ITT to Non-ITT cohorts by intervention group

Intervention Group	Intent-To-Treat (ITT) (N)	Non-Intent-To-Treat (Non-ITT) (N)	% Decrease from ITT to Non-ITT
ODA	4,645	3,845	17.22
ODAHRT	4,391	3,797	13.53
ODHRT	1,620	1,054	34.94
ODNOTX	7,568	4,313	43.01
NOODTX	31,627	25,274	20.09
Total	49,851	38,283	23.21

FREQUENCY DISTRIBUTIONS AND DESCRIPTIVE STATISTICS

The following sub-section reports the frequency distributions and where appropriate descriptive statistics of the dependent and independent variables for both the intent-to-treat cohort and non intent-to-treat cohort. To facilitate the comparison between cohorts, the frequency distributions and descriptive statistics for the non intent-to-treat cohort will immediately follow those of the intent-to-treat cohort for the dependent and each independent variable. Reported first are frequency distributions of the dependent variables.

Dependent Variable

Intent-To-Treat Cohort

In the intent-to-treat analysis, a total of 1,812 fracture events were reported during the study (assessment period 574; observation period 1,238). Tables 3.2 and 3.3 show the

frequency distributions of fracture type for the study and observation periods, respectively. During the observation period, vertebral fracture was the most commonly reported fracture type (39.42%), followed by wrist (34.89%) and hip fracture (25.69%).

Table 3.2 ITT: Frequency distribution of fractures by fracture type during study

Fracture Type	Frequency N = Fractures	Percent	Cumulative Frequency	Cumulative Percent
Hip	525	28.97	525	28.97
Vertebral	574	31.68	1,099	60.65
Wrist	713	39.35	1,812	100.00

Table 3.3 ITT: Frequency distribution of fractures by fracture type during observation period

Fracture Type	Frequency N = Fractures	Percent	Cumulative Frequency	Cumulative Percent
Hip	318	25.69	318	25.69
Vertebral	488	39.42	806	65.11
Wrist	432	34.89	1,238	100.00

Table 3.4 shows the frequency distribution of patients who experienced a fracture event during the assessment period and each observation year by fracture type. More patients experienced a fracture event during the third observation year (510) than in the previous two observation years (first observation year 320; second observation year 354). The proportion of patients who experienced a fracture event during any observation year ranged from 0.64% to 1.02%, with less than 0.05% experiencing multiple fractures.

Table 3.4 ITT: Frequency distribution of the cohort by fracture type for the assessment period and each observation year

Fracture Type	Frequency N = Patients	Percent	Cumulative Frequency	Cumulative Percent
Assessment Period				
None	49,302	98.90	49,302	98.90
Hip	188	0.38	49,490	99.28
Vertebral	77	0.15	49,567	99.43
Wrist	259	0.52	49,826	99.95
Hip & Vertebral	3	0.01	49,829	99.96
Hip & Wrist	16	0.03	49,845	99.99
Vertebral & Wrist	6	0.01	49,851	100.00
Observation Year 1				
None	49,531	99.36	49,531	99.36
Hip	68	0.14	49,599	99.49
Vertebral	118	0.24	49,717	99.73
Wrist	125	0.25	49,842	99.98
Hip & Vertebral	5	0.01	49,847	99.99
Hip & Wrist	3	0.01	49,850	100.00
Vertebral & Wrist	1	0.00	49,851	100.00
Observation Year 2				
None	49,497	99.29	49,497	99.29
Hip	87	0.17	49,584	99.46
Vertebral	120	0.24	49,704	99.71
Wrist	133	0.27	49,837	99.97
Hip & Vertebral	5	0.01	49,842	99.98
Hip & Wrist	4	0.01	49,846	99.99
Vertebral & Wrist	4	0.01	49,850	100.00
Hip, Vertebral & Wrist	1	0.00	49,851	100.00
Observation Year 3				
None	49,341	98.98	49,341	98.98
Hip	131	0.26	49,472	99.24
Vertebral	213	0.43	49,685	99.67
Wrist	145	0.29	49,830	99.96
Hip & Vertebral	6	0.01	49,836	99.97
Hip & Wrist	4	0.01	49,840	99.98
Vertebral & Wrist	10	0.02	49,850	100.00
Hip, Vertebral & Wrist	1	0.00	49,851	100.00

Non Intent-To-Treat Cohort

In the non intent-to-treat analysis a total of 1,145 fracture events were reported during the study (assessment period 408; observation period 737). Tables 3.5 and 3.6 show the frequency distributions of fracture type for the study and observation periods, respectively. Wrist fracture was the most commonly reported fracture type (38.53%), followed by vertebral (32.29%) and hip fracture (29.17%) during the observation period.

Table 3.5 Non-ITT: Frequency distribution of fractures by fracture type during study

Fracture Type	Frequency N = Fractures	Percent	Cumulative Frequency	Cumulative Percent
Hip	361	31.53	361	31.53
Vertebral	299	26.11	660	57.64
Wrist	485	42.36	1,145	100.00

Table 3.6 Non-ITT: Frequency distribution of fractures by fracture type during observation period

Fracture Type	Frequency N = Fractures	Percent	Cumulative Frequency	Cumulative Percent
Hip	215	29.17	215	29.17
Vertebral	238	32.29	453	61.47
Wrist	284	38.53	737	100.00

Table 3.7 shows the frequency distribution of patients who experienced a fracture event during the assessment period and for each observation year by fracture type. More patients experienced a fracture event during the third observation year (288) than in the previous two observation years (first observation year 206; second observation year 216). The proportion of patients who experienced a fracture event during any observation year

ranged from 0.54% to 0.75%. Less than 0.05% of patients experienced multiple fractures within a given observation year.

Table 3.7 Non-ITT: Frequency distribution of the cohort by fracture type during the assessment period and each observation year

Fracture Type	Frequency N = Patients	Percent	Cumulative Frequency	Cumulative Percent
Assessment Period				
None	37,894	98.98	37,894	98.98
Hip	131	0.34	38,025	99.33
Vertebral	55	0.14	38,080	99.47
Wrist	184	0.48	38,264	99.95
Hip & Vertebral	2	0.01	38,266	99.96
Hip & Wrist	13	0.03	38,279	99.99
Vertebral & Wrist	4	0.01	38,283	100.00
Observation Year 1				
None	38,077	99.46	38,077	99.46
Hip	51	0.13	38,128	99.60
Vertebral	66	0.17	38,194	99.77
Wrist	86	0.22	38,280	99.99
Hip & Vertebral	3	0.22	38,283	100.00
Observation Year 2				
None	38,067	99.44	38,067	99.44
Hip	67	0.18	38,134	99.61
Vertebral	56	0.15	38,190	99.76
Wrist	84	0.22	38,274	99.98
Hip & Vertebral	2	0.01	38,276	99.98
Hip & Wrist	3	0.01	38,279	99.99
Vertebral & Wrist	4	0.01	38,283	100.00
Observation Year 3				
None	37,995	99.25	37,995	99.25
Hip	82	0.21	38,077	99.46
Vertebral	98	0.26	38,175	99.72
Wrist	98	0.26	38,273	99.97
Hip & Vertebral	2	0.01	38,275	99.98
Hip & Wrist	3	0.01	38,278	99.99
Vertebral & Wrist	5	0.01	38,283	100.00

Comparing the intent-to-treat cohort to the non intent-to-treat cohort, the two cohorts were similar in that more fracture events were reported during the third observation year than in the previous two years. However, the two cohorts differed in the proportion of patients who experienced any type of fracture and also in the most commonly reported fracture type. The proportion of patients who experienced any type of fracture was higher in the intent-to-treat cohort compared to the non intent-to-treat cohort. Vertebral fracture was the most commonly reported fracture event in the intent-to-treat cohort, whereas wrist fracture was the most commonly reported fracture event in the non intent-to-treat cohort.

Independent Variables

The independent variables collected from prescription and health claims data included age, previous osteoporotic fracture, corticosteroid use, statin use, and intervention compliance. The frequency distributions and descriptive statistics of the independent variables are provided below.

Age

Intent-To-Treat Cohort

The mean age of the intent-to-treat cohort was 63.05 years (SD = 8.94). A general linear model showed significant differences in mean age between the intervention groups $F(4, 49,846) = 207.50, p < 0.0001$. Application of Duncan's multiple-range test revealed that significant differences exist in mean age between each intervention group except for the ODNOTX and NOODTX intervention groups. Table 3.8 shows the descriptive statistics of patient age for the cohort and intervention groups.

Table 3.8 ITT: Descriptive statistics of patient age for the cohort and intervention groups

Intervention Group	N = Patients	Mean Age	Standard Deviation	Minimum	Maximum
ODA	4,645	66.69	8.50	50.00	93.00
ODAHRT	4,391	63.66	7.60	50.00	90.00
ODHRT	1,620	59.96	6.44	50.00	92.00
ODNOTX	7,568	62.41	8.26	50.00	96.00
NOODTX	31,627	62.74	9.29	50.00	99.00
Cohort	49,851	63.05	8.94	50.00	99.00

* F (4, 49,846) = 207.50, p < 0.0001

Objectives one through four categorize patients into age categories; therefore; the distribution of patients by intervention group and age categories was examined. A Chi-Square test for independence revealed that the relationship between intervention groups and age categories was not independent χ^2 (28, n = 49,851) = 2713.87, p < 0.0001. Examination of observed cell frequencies vs. expected cell frequencies and cell chi-squares revealed significant differences for the distribution of patients by intervention group and age category. In fact, the ODA and ODHRT intervention groups had opposite age category distributions. The ODA intervention group had lower than expected cell frequencies for the first three age categories and higher than expected cell frequencies in the last five age categories, whereas the ODHRT intervention group had higher than expected cell frequencies first three age categories and a lower than expected cell frequencies in the last five age categories. In other words, the ODA intervention group had a higher distribution of older patients compared to the ODHRT intervention group. No significant distribution pattern of age categories was noted for the other intervention groups. Table 3.9 shows the distribution of the cohort by intervention groups and age categories.

Table 3.9 ITT: Frequency distribution of cohort by intervention group and age categories

Frequency Expected Cell Chi-Square Row %		Age Categories								Total
		50 to 54	55 to 59	60 to 64	65 to 69	70 to 74	75 to 79	80 to 84	85 Plus	
Intervention Group	ODA	336	610	1,150	865	709	632	256	87	4,645
		872.14	880.72	1,222.6	636.22	421.44	369.45	161.38	81.07	9.32
		329.59	83.21	4.31	82.27	196.21	186.58	55.47	0.43	
		7.23	13.13	24.76	18.62	15.26	13.61	5.51	1.87	
	ODAHRT	517	815	1,284	852	459	352	85	27	4,391
		824.45	832.56	1,155.7	601.43	398.40	349.25	152.56	76.63	8.81
		114.65	0.37	14.24	104.40	9.22	0.02	29.92	32.15	
		11.77	18.56	29.24	19.40	10.45	8.02	1.94	0.61	
	ODHRT	341	452	605	97	57	54	9	5	1,620
		304.17	307.16	426.39	221.89	146.98	128.85	56.29	28.72	3.25
		4.46	68.30	74.82	70.30	55.09	43.48	39.72	19.16	
		21.05	27.90	37.35	5.99	3.52	3.33	0.56	0.31	
	ODNOTX	1,142	1,710	2,822	625	434	455	238	142	7,568
		1,421	1,434.90	1,991.90	1,036.60	686.65	601.94	262.94	132.08	15.18
		54.77	52.73	345.90	163.42	92.96	35.87	2.37	0.75	
		15.09	22.60	37.29	8.26	5.73	6.01	3.14	1.88	
	NOODTX	7,024	5,865	7,260	4,389	2,864	2,472	1,144	609	31,627
		5,938.30	5,996.60	8,324.4	4,331.90	2,869.5	2,515.5	1,098.8	551.95	63.44
		198.51	2.89	136.09	0.75	0.01	0.75	1.86	5.90	
		22.21	18.54	22.96	13.88	9.06	7.82	3.62	1.93	
Total		9,360	9,452	13,121	6,828	4,532	3,965	1,732	870	49,851
		18.78	18.96	26.32	13.70	9.07	7.95	3.47	1.75	100.00

* χ^2 (28, n = 49,851) = 2713.87, p < 0.0001

Non Intent-To-Treat Cohort

The mean age of the non intent-to-treat cohort was 63.32 (SD = 9.12). A general linear model showed significant differences in mean age between the intervention groups $F(4, 38,278) = 204.47, p < 0.0001$. Application of Duncan's multiple-range test revealed that significant differences exist in mean age between each intervention group except for the ODNOTX and NOODTX intervention groups. Table 3.10 shows the descriptive statistics of patient age for the cohort and intervention groups.

Table 3.10 Non-ITT: Descriptive statistics of patient age for the cohort and intervention groups

Intervention Group	N Observations	Mean Age	Standard Deviation	Minimum	Maximum
ODA	3,845	66.81	8.54	50.00	93.00
ODAHRT	3,797	63.56	7.58	50.00	89.00
ODHRT	1,054	59.40	6.19	50.00	92.00
ODNOTX	4,313	63.07	8.87	50.00	96.00
NOODTX	25,274	62.97	9.41	50.00	99.00
Cohort	38,283	63.32	9.12	50.00	99.00

* $F(4, 38,278) = 204.47, p < 0.0001$

A Chi-square test for independence revealed that the relationship between intervention groups and age categories was not independent $\chi^2(28, n = 38,283) = 1,800.95, p < 0.0001$. As observed in the intent-to-treat cohort, the ODA and ODHRT intervention groups had opposite age category distributions. Table 3.11 shows the distribution of the cohort by intervention groups and age categories.

Table 3.11 Non-ITT: Frequency distribution of the cohort by intervention group and age categories

Frequency Expected Cell Chi-Square Row %		Age Categories								Total
		50 to 54	55 to 59	60 to 64	65 to 69	70 to 74	75 to 79	80 to 84	85 Plus	
Intervention Group	ODA	275	508	928	708	594	544	214	74	3,845
		707.47	721.43	970.11	541.35	365.19	320.79	142.42	76.23	10.04
		264.37	63.14	1.83	51.30	143.37	155.31	35.98	0.07	
		7.15	13.21	24.14	18.41	15.45	14.15	5.57	1.92	
	ODAHRT	455	728	1,087	738	399	299	71	20	3,797
		698.64	712.43	958	534.59	360.63	316.79	140.64	75.28	9.92
		84.97	0.34	17.37	77.39	4.08	1.00	34.48	40.59	
		11.98	19.17	28.63	19.44	10.51	7.87	1.87	0.53	
	ODHRT	248	310	377	52	33	29	2	3	1,054
		193.93	197.76	265.93	148.4	100.11	87.94	39.04	20.90	2.75
		15.07	63.70	46.39	62.62	44.98	39.50	35.14	15.33	
		23.53	29.41	35.77	4.93	3.13	2.75	0.19	0.28	
	ODNOTX	657	908	1,485	394	281	312	165	111	4,313
		793.58	809.24	1,088.20	607.24	409.64	359.84	159.75	85.51	11.27
		23.51	12.05	144.70	74.88	40.40	6.36	0.17	7.60	
		15.23	21.05	34.43	9.14	6.52	7.23	3.83	2.57	
	NOODTX	5,409	4,729	5,782	3,498	2,329	2,010	966	551	25,274
		4,650.40	4,742.10	6,376.80	3,558.40	2,400.40	2,108.60	936.15	501.08	66.02
		123.76	0.04	55.47	1.03	2.13	4.61	0.95	4.97	
		21.40	18.71	22.88	13.84	9.22	7.95	3.82	2.18	
Total		7,044	7,183	9,659	5,390	3,636	3,194	1,418	759	38,283
		18.40	18.76	25.23	14.08	9.50	8.34	3.70	1.98	100.00

* χ^2 (28, n = 38,283) = 1800.95, p < 0.0001

With respect to the independent variable age, the intent-to-treat cohort and the non intent-to-treat cohorts were similar.

Previous Osteoporotic Fracture

Intent-To-Treat Cohort

A total of 549 (1.10%) patients in the intent-to-treat cohort experienced a fracture during the assessment period and were thereby coded as having a previous osteoporotic fracture event. A Chi-Square test for independence revealed that the relationship between intervention groups and previous osteoporotic fracture was not independent $\chi^2(4, n = 49,851) = 933.02, p < 0.0001$. Examination of observed cell frequencies vs. expected cell frequencies and cell chi-squares revealed significant differences for the distribution of patients with a previous osteoporotic fracture by intervention group. The ODA, ODAHRT, ODHRT, and ODNOTX intervention groups, or those with a diagnosis of osteoporosis, had higher than expected frequency of previous osteoporotic fracture, whereas the NOODTX intervention group had a lower than expected frequency of previous osteoporotic fracture. Table 3.12 shows the frequency distribution of the cohort by intervention groups and previous osteoporotic fracture.

Table 3.12 ITT: Frequency distribution of the cohort by intervention group and previous osteoporotic fracture

Frequency Expected Cell Chi-Square Row %		Previous Osteoporotic Fracture		Total
		No	Yes	
Intervention Group	ODA	4,488 4,593.80 2.44 96.62	157 51.55 219.01 3.38	4,645 9.32
	ODAHRT	4,261 4,342.60 1.53 97.04	130 48.36 137.84 2.96	4,391 8.81
	ODHRT	1,562 1,602.20 1.01 96.42	58 17.84 90.40 3.58	1,620 3.25
	ODNOTX	7,374 7,484.70 1.64 97.44	194 83.35 146.91 2.56	7,568 15.18
	NOODTX	31,617 31,279 3.66 99.97	10 348.30 328.59 0.03	31,627 63.44
Total		49,302 98.90	549 1.10	49,851 100.00

* χ^2 (4, n= 49,851) = 933.02, p < 0.0001

Non Intent-To-Treat Cohort

A total of 389 (1.02%) patients in the non intent-to-treat cohort experienced a fracture during the assessment period and were thereby coded as having a previous osteoporotic fracture event. A Chi-Square test for independence revealed that the relationship between intervention groups and previous osteoporotic fracture was not independent χ^2 (4, n= 38,283) = 734.48, p <0.0001. Examination of observed cell frequencies vs. expected cell frequencies and cell chi-squares revealed significant

differences for the distribution of patients with a previous osteoporotic fracture by intervention group. As with the intent-to-treat cohort, the ODA, ODAHRT, ODHRT, and ODNOTX intervention groups had higher than expected frequency of previous osteoporotic fracture, whereas the NOODTX intervention group had a lower than expected frequency of previous osteoporotic fracture. Table 3.13 shows the frequency distribution of the cohort by intervention groups and previous osteoporotic fracture.

Table 3.13 Non-ITT: Frequency distribution of the cohort by intervention group and previous osteoporotic fracture

Frequency Expected Cell Chi-Square Row %		Previous Osteoporotic Fracture		Total
		No	Yes	
Intervention Group	ODA	3,713 3,805.90 2.27 96.57	132 39.07 221.04 3.43	3,845 10.04
	ODAHRT	3,692 3,758.40 1.17 97.23	105 38.58 114.34 2.77	3,797 9.92
	ODHRT	1,020 1,043.30 0.52 96.77	34 10.71 50.65 3.23	1,054 2.75
	ODNOTX	4,203 4,269.20 1.03 97.45	110 43.83 99.92 2.55	4,313 11.27
	NOODTX	25,266 25,017 2.47 99.97	8 256.81 241.06 0.03	25,274 66.02
Total		37,894 98.98	389 1.02	38,283 100.00

* χ^2 (4, n= 38,283) = 734.48, p < 0.0001

The intent-to-treat and non intent-to-treat cohorts were similar in regards to the distribution of patients in the intervention groups with a previous osteoporotic fracture. The higher than expected cell frequencies of patients with previous osteoporotic fracture in the ODA, ODAHRT, ODHRT, and ODNOTX intervention groups was consistent for both intervention groups, with little variance in row percentages between cohorts.

Corticosteroid Use

Intent-To-Treat Cohort

In the intent-to-treat cohort, a total of 9,797 (19.65%) patients used an oral corticosteroid during the study (assessment period and/or observation period). A chi-square test for independence revealed that the relationship between intervention groups and oral corticosteroid use was not independent $\chi^2 (4, n = 49,851) = 603.56, p < 0.0001$. Examination of observed cell frequencies vs. expected cell frequencies and cell chi-squares revealed significant differences for the distribution of patients who used an oral corticosteroid by intervention group. A frequency distribution pattern similar to the previous (intervention group by previous osteoporotic fracture) was observed for corticosteroid use. The ODA, ODAHRT, ODHRT, and ODNOTX intervention groups, or those with a diagnosis of osteoporosis, had a higher than expected cell frequencies of oral corticosteroid use, whereas the NOODTX intervention group had a lower than expected cell frequency of oral corticosteroid use. From a different perspective, oral corticosteroid users were more likely to have a diagnosis of osteoporosis. An additional noteworthy difference was that although the ODNOTX intervention group had a higher than expected cell frequency of oral corticosteroid use, relative to the other osteoporosis

diagnosis intervention groups, the ODNOTX intervention group had a smaller row percentage and cell chi-square, indicating fewer oral corticosteroid users relative to the other intervention groups. The corticosteroid use cell chi-square for the ODAHRT intervention contributed most to the overall chi-square. Table 3.14 shows the frequency distribution of the cohort by intervention group and oral corticosteroid use.

Table 3.14 ITT: Frequency distribution of the cohort by intervention group and oral corticosteroid use

Frequency Expected Cell Chi-Square Row %		Corticosteroid Use		Total
		No	Yes	
Intervention Group	ODA	3,461 3,732.10 19.70 74.51	1,184 912.86 80.53 25.49	4,645 9.32
	ODAHRT	3,077 3,528.10 57.67 70.08	1,314 862.94 235.76 29.92	4,391 8.81
	ODAHRT	1,213 1,301.60 6.03 74.88	407 318.37 24.67 25.12	1,620 3.25
	ODNOTX	5,972 6,080.70 1.94 78.91	1,596 1,487.30 7.94 21.09	7,568 15.18
	NOODTX	26,331 25,411 33.27 83.25	5,296 6,215.50 136.03 16.75	31,627 63.44
Total		40,054 80.35	9,797 19.65	49,851 100.00

* χ^2 (4, n = 49,851) = 603.56, p < 0.0001

The above frequency distribution describes the distribution of intervention groups by oral corticosteroid use. However, as previously described, this study assesses the impact of this risk factor by categorizing oral corticosteroid use by dose and duration. Therefore, of more interest, is the distribution of patients by oral corticosteroid dose and duration categories and intervention groups (patients not on an oral corticosteroid were excluded from the analysis). A chi-square test for independence showed that the relationship between intervention groups and oral corticosteroid dose and duration categories was not independent $\chi^2 (44, n = 9,797) = 469.86, p < 0.0001$. Examination of observed cell frequencies vs. expected cell frequencies and cell chi-squares revealed significant differences for the distribution of patients by corticosteroid dose and duration categories within each intervention group and between intervention groups. In general, active intervention groups (ODA, ODAHRT, and ODHRT) had higher than expected cell frequencies for the oral corticosteroid dose and duration categories, where corticosteroid duration exceeded one-year, indicating that long-term oral corticosteroid users were more likely to receive an active intervention. Table 3.15 shows the distribution of the cohort by intervention group and corticosteroid dose and duration categories.

Table 3.15 ITT: Frequency distribution of the cohort by intervention group and oral corticosteroid dose and duration categories

Frequency Expected Cell Chi-Square Row (%)		Dose (mg) by Duration (days)					
		<5mg ≤180 days	<5mg >180≤365 days	<5mg >365 days	≥5≤10mg ≤180 days	≥5≤10mg >180≤365 days	≥5≤10mg >365 days
Intervention Group	ODA	50	2	76	188	27	130
		59.70	4.59	51.85	203.03	27.19	86.05
		1.58	1.46	11.25	1.11	0.01	22.45
		4.22	0.17	6.42	15.88	2.28	10.98
	ODAHRT	72	5	108	205	39	164
		66.26	5.10	57.54	225.33	30.18	95.50
		.50	0.02	44.25	1.83	2.58	49.14
		5.48	0.38	8.22	15.60	2.97	12.48
	ODHRT	25	2	19	68	6	31
		20.52	1.58	17.82	69.79	9.35	29.58
		0.98	0.11	0.08	0.05	1.20	0.07
		6.14	0.49	4.67	16.71	1.47	7.62
	ODNOTX	77	5	107	241	38	179
		80.48	6.19	69.89	273.68	36.65	115.99
		0.15	0.23	19.71	3.90	0.05	34.23
		4.82	0.31	6.70	15.10	2.38	11.22
	NOODTX	270	24	119	978	115	208
		267.04	20.54	231.91	908.16	121.63	384.89
		0.03	0.58	54.97	5.37	0.36	81.29
		5.10	0.45	2.25	18.47	2.17	3.93
Total		494	38	429	1,680	225	712
		5.04	0.39	4.38	17.15	2.30	7.27

* χ^2 (44, n = 9,797) = 469.86, p < 0.0001

Table 3.15 ITT: Frequency distribution of the cohort by intervention group and oral corticosteroid dose and duration categories (cont'd)

Frequency Expected Cell Chi-Square Row (%)		Dose (mg) by Duration (days)						Total
		>10≤20mg ≤180 days	>10≤20mg >180≤365 days	>10≤20mg >365 days	≥20mg ≤180 days	≥20mg >180≤365 days	≥20mg >365 days	
Intervention Group	ODA	203	27	55	399	16	11	1,184
		238.81	23.57	36.26	433.50	13.78	5.68	12.09
		5.37	0.50	9.69	2.75	0.36	4.98	
		17.15	2.28	4.65	33.70	1.35	0.93	
	ODAHRT	258	24	61	355	14	9	1,314
		265.03	26.15	40.24	481.1	15.29	6.30	13.41
		0.19	0.18	10.71	33.05	0.11	1.15	
		19.63	1.83	4.64	27.02	1.07	0.68	
	ODHRT	83	9	16	145	3	0	407
		82.09	8.10	12.46	149.02	4.74	1.95	4.15
		0.01	0.10	1.00	0.11	0.64	1.95	
		20.39	2.21	3.93	35.63	0.74	0.00	
	ODNOTX	280	36	60	553	15	5	1,596
		321.90	31.77	48.87	584.35	18.57	7.66	16.29
		5.45	0.56	2.53	1.68	0.69	0.92	
		17.54	2.26	3.76	34.65	0.94	0.31	
	NOODTX	1,152	99	108	2,135	66	22	5,296
		1,068.20	105.41	162.17	1,939	61.63	25.41	54.06
		6.58	0.39	18.10	19.80	0.31	0.46	
		21.57	1.87	2.04	40.31	1.25	0.42	
Total		1,976	195	300	3,587	114	47	9,797
		20.17	1.99	3.06	36.61	1.16	0.48	100.00

* χ^2 (44, n = 9,797) = 469.86, p < 0.0001

Non Intent-To-Treat Cohort

In the non intent-to-treat cohort, a total of 7,193 (18.79%) patients used an oral corticosteroid during the study (assessment period and/or observation period). A chi-square test for independence revealed that the relationship between intervention groups and oral corticosteroid use was not independent $\chi^2 (4, n = 38,283) = 530.83, p < 0.0001$. Examination of observed cell frequencies vs. expected cell frequencies and cell chi-squares revealed significant differences for the distribution of patients who used an oral corticosteroid by intervention group. The same oral corticosteroid use distributional differences observed for the intent-to-treat cohort were present in the non intent-to-treat cohort. Table 3.16 shows the frequency distribution of the cohort by intervention group and by oral corticosteroid use.

Table 3.16 Non-ITT: Frequency distribution of the cohort by intervention group and oral corticosteroid use

Frequency Expected Cell Chi-Square Row %		Corticosteroid Use		Total
		No	Yes	
Intervention Group	ODA	2,878	967	3,845
		3,122.60	722.44	10.04
		19.15	82.79	
		74.85	25.15	
	ODAHRT	2,682	1,115	3,797
		3,083.60	713.42	9.92
		52.30	226.05	
		70.63	29.37	
	ODHRT	808	246	1,054
		855.96	198.04	2.75
		2.69	11.62	
		76.66	23.34	
	ODNOTX	3,475	838	4,313
		3,502.60	810.37	11.27
		0.22	0.94	
		80.57	19.43	
	NOODTX	21,247	4,027	25,274
		20,525	4,748.70	66.02
		25.38	109.69	
		84.07	15.93	
Total		31,090	7,193	38,283
		81.21	18.79	100.00

* χ^2 (4, n = 38,283) = 530.83, p < 0.0001

Table 3.17 shows the frequency distribution of the cohort by intervention group and oral corticosteroid dose and duration categories. A chi-square test for independence showed that the relationship between intervention groups and oral corticosteroid dose and duration categories was not independent χ^2 (44, n = 7,193) = 385.04, p < 0.0001. In the non intent-to-treat cohort, only the ODA and ODAHRT intervention groups had higher than expected cell frequencies in oral corticosteroid dose and duration categories, where corticosteroid duration exceeded one-year.

Table 3.17 Non-ITT: Frequency distribution of the cohort by intervention group and oral corticosteroid dose and duration categories

Frequency Expected Cell Chi-Square Row %		Dose (mg) by Duration (days)					
		<5mg ≤180 days	<5mg >180≤365 days	<5mg >365 days	≥5≤10mg ≤180 days	≥5≤10mg >180≤365 days	≥5≤10mg >365 days
Intervention Group	ODA	37	2	66	151	19	103
		48.80	3.63	39.39	167.64	21.38	65.20
		2.85	0.73	17.98	1.65	0.26	21.91
		3.83	0.21	6.83	15.62	1.96	10.65
	ODAHRT	65	3	90	178	30	139
		56.27	4.19	45.42	193.30	24.65	75.18
		1.35	0.34	43.76	1.21	1.16	54.17
		5.83	0.27	8.07	15.96	2.69	12.47
	ODHRT	14	1	12	44	4	17
		12.41	0.92	10.02	42.65	5.44	16.59
		0.20	0.01	0.39	0.04	0.38	0.01
		5.69	0.41	4.88	17.89	1.63	6.91
	ODNOTX	40	2	40	124	18	88
		42.29	3.15	34.13	145.28	18.52	56.50
		0.12	0.42	1.01	31.12	0.01	17.56
		4.77	0.24	4.77	14.80	2.15	10.50
	NOODTX	207	19	85	750	88	138
		203.23	15.12	164.04	698.13	89.02	271.53
		0.07	1.00	38.08	3.85	0.01	65.66
		5.14	0.47	2.11	18.62	2.19	3.43
Total		363	27	293	1,247	159	485
		5.05	0.38	4.07	17.34	2.21	6.74

* χ^2 (44, n = 7,193) = 385.04, p < .0001

Table 3.17 Non-ITT: Frequency distribution of the cohort by intervention group and oral corticosteroid dose and duration categories (cont'd)

Frequency Expected Cell Chi-Square Row (%)		Dose (mg) by Duration (days)						Total
		>10≤20mg ≤180 days	>10≤20mg >180≤365 days	>10≤20mg > 365 days	≥20mg ≤180 days	≥20mg >180≤365 days	≥20mg >365 days	
Intervention Group	ODA	166	20	44	341	11	7	967
		195.74	19.49	28.64	361.77	10.62	4.71	13.44
		4.52	0.01	8.24	1.19	0.01	1.12	
		17.17	2.07	4.55	35.26	1.14	0.72	
	ODAHRT	214	18	53	306	11	8	1,115
		225.70	22.48	33.02	417.14	12.25	5.43	15.50
		0.61	0.89	12.09	29.61	0.13	1.22	
		19.19	1.61	4.75	27.44	0.99	0.72	
	ODHRT	44	6	8	96	0	0	246
		49.80	4.96	7.28	92.03	2.70	1.20	3.42
		.67	.22	0.07	0.17	2.70	1.20	
		17.89	2.44	3.25	39.02	0.00	0.00	
	ODNOTX	158	25	31	302	7	3	838
		169.63	16.89	24.82	313.51	9.20	4.08	11.65
		0.80	3.89	1.54	0.42	0.53	.28	
		18.85	2.98	3.70	36.04	0.84	0.36	
	NOODTX	874	76	77	1,646	50	17	4,027
		815.14	81.18	119.25	1506.60	44.23	19.60	55.98
		4.25	0.33	14.97	12.91	0.75	0.34	
		21.70	1.89	1.91	40.87	1.24	0.42	
Total		1,456	145	213	2,691	79	35	7,193
		20.24	2.02	2.96	37.41	1.10	0.49	100.00

* χ^2 (44, n = 7,193) = 385.04, p < .0001

Statin Use

Intent-To-Treat Cohort

In the intent-to-treat cohort, a total of 16,665 (33.41%) patients used a statin during the study (assessment period and/or observation period). A chi-square test for independence revealed that the relationship between intervention groups and statin use was not independent $\chi^2 (4, n = 49,851) = 168.49, p < 0.0001$. Examination of observed cell frequencies vs. expected cell frequencies and cell chi-squares revealed significant differences for the distribution of patients who used a statin by intervention group for the ODA and NOODTX intervention groups. The ODA intervention group had a higher than expected cell frequency of statin use, whereas the NOODTX intervention group had a lower than expected cell frequency of statin use. Table 3.18 shows the frequency distribution of the cohort by intervention group and statin use.

Table 3.18 ITT: Frequency distribution of the cohort by intervention group and statin use

Frequency Expected Cell Chi-Square Row %		Statin Use		Total
		No	Yes	
Intervention Group	ODA	2,747 3,093.10 38.73 59.14	1,898 1,551.90 77.20 40.86	4,645 9.32
	ODAHRT	2,921 2,924 0.00 66.52	1,470 1,467 0.00 33.48	4,391 8.81
	ODHRT	1,066 1,078.80 0.15 65.80	554 541.23 0.30 34.20	1,620 3.25
	ODNOTX	4,885 5,039.60 4.74 64.55	2,683 2,528.40 9.45 35.45	7,568 15.18
	NOODTX	21,577 21,061 12.66 68.22	10,050 10,566 25.24 31.78	31,627 63.44
Total		33,196 66.59	16,655 33.41	49,851 100.00

* χ^2 (4, n = 49,851) = 168.49, p < 0.0001

As with oral corticosteroid use, this study assesses the impact of this risk factor by categorizing statin use by dose and duration. A chi-square test for independence showed that the relationship between intervention groups and statin dose and duration categories was not independent χ^2 (20, n = 16,655) = 381.15, p < 0.0001. Examination of observed cell frequencies vs. expected cell frequencies and cell chi-squares revealed significant differences for the distribution of patients by statin dose and duration categories for intervention groups ODA, ODAHRT and NOODTX. The ODA and ODAHRT

intervention groups had higher than expected cell frequencies in the low dose duration > 2-years category and the high dose duration > 2-years category whereas the ODNOTX intervention group had a lower than expected cell frequencies in the same statin dose and duration categories. Other statin dose and duration category distributional differences were not overtly apparent for the other intervention groups. Table 3.19 shows the frequency distribution of the cohort by intervention group and statin dose and duration categories.

Table 3.19 ITT: Frequency distribution of the cohort by intervention group and statin dose and duration categories

Frequency Expected Cell Chi-Square Row (%)		Dose Category (Low, High) by Duration (Years)						Total
		Low ≤1 year	Low >1≤2 years	Low >2 years	High ≤1 year	High >1≤2 years	High >2 years	
Intervention Group	ODA	455	308	728	89	85	233	1,898
		550.08	369	523.99	149.97	125.7	179.26	11.40
		16.44	10.08	79.43	24.79	13.18	16.11	
		23.97	16.23	38.36	4.69	4.48	12.28	
	ODAHRT	344	257	567	80	59	163	1,470
		426.04	285.79	405.83	116.15	97.35	138.84	8.83
		15.80	2.90	64.01	11.25	15.11	4.21	
		23.40	17.48	38.57	5.44	4.01	11.09	
	ODHRT	131	110	177	42	37	57	554
		160.56	107.71	152.94	43.77	36.69	52.32	3.33
		5.44	0.05	3.78	0.07	0.00	0.42	
		23.65	19.86	31.95	7.58	6.68	10.29	
	ODNOTX	746	535	721	243	189	249	2,683
		777.59	521.62	740.7	212	177.69	253.40	16.11
		1.28	0.34	0.52	4.53	0.72	0.08	
		27.80	19.94	26.87	9.06	7.04	9.28	
	NOODTX	3,151	2,028	2,405	862	733	871	10,050
		2,912.70	1,953.90	2,774.50	794.10	665.57	949.18	60.34
		19.49	2.82	49.22	5.81	6.83	6.44	
		31.35	20.18	23.93	8.58	7.29	8.67	
Total		4,827	3,238	4,598	1,316	1,103	1,573	16,655
		28.98	19.44	27.61	7.90	6.62	9.44	100.00

* χ^2 (20, n = 16,655) = 381.15, p < 0.0001

Non Intent-To-Treat Cohort

In the non intent-to-treat cohort, a total of 12,473 (32.58%) patients used a statin during the study (assessment period and/or observation period). A chi-square test for independence revealed that the relationship between intervention groups and statin use was not independent $\chi^2 (4, n = 38,283) = 178.84, p < 0.0001$. The significant differences observed for the distribution paralleled those of the intent-to-treat cohort. Table 3.20 shows the frequency distribution of the cohort by intervention group and statin use.

Table 3.20 Non- ITT: Frequency distribution of intervention group by statin use

Frequency Expected Cell Chi-Square Row %		Statin Use		Total
		No	Yes	
Intervention Group	ODA	2,258	1,587	3,845
		2,592.30	1,252.70	10.04
		43.10	89.19	
		58.73	41.27	
	ODAHRT	2,533	1,264	3,797
		2,559.90	1,237.10	9.92
		0.28	0.58	
		66.71	33.29	
	ODHRT	696	358	1,054
		710.60	343.40	2.75
		0.30	0.62	
		66.03	33.97	
	ODNOTX	2,826	1,487	4,313
		2,907.8	1,405.20	11.27
		2.3	4.76	
		65.52	34.48	
	NOODTX	17,497	7,777	25,274
		17,039	8,234.50	66.02
		12.29	25.42	
		69.23	30.77	
Total		25,810	12,473	38,283
		67.42	32.58	100.00

* χ^2 (4, n = 38,283) = 178.84, p < 0.0001

A chi-square test for independence showed that the relationship between intervention groups and statin dose and duration categories was not independent χ^2 (20, n = 16,655) = 278.74, p < 0.0001. Examination of observed cell frequencies vs. expected cell frequencies and cell chi-squares revealed the same significant differences for the distribution of patients by statin dose and duration categories for intervention groups ODA, ODAHRT and NOODTX as observed in the intent-to-treat cohort. Table 3.21

shows the frequency distribution of the cohort by intervention group and statin dose and duration categories.

Table 3.21 Non-ITT: Frequency distribution of the cohort by intervention group and statin dose and duration categories

Frequency Expected Cell Chi-Square Row (%)		Dose Category (Low, High) by Duration (Years)						Total
		Low ≤1	Low >1≤2	Low >2	High ≤1	High >1≤2	High >2	
Intervention Group	ODA	388	260	602	79	64	194	1,587
		460.97	302.44	451.17	123.29	98.10	151.03	12.72
		11.55	5.95	50.42	15.91	11.85	12.23	
		24.45	16.38	37.93	4.98	4.03	12.22	
	ODAHRT	290	228	485	69	52	140	1,264
		367.15	240.88	359.35	98.20	78.13	120.29	10.13
		16.21	0.69	43.94	8.68	8.74	3.23	
		22.94	18.04	38.37	5.46	4.11	11.08	
	ODHRT	90	67	118	30	19	34	358
		103.99	68.23	101.78	27.81	22.12	34.07	2.87
		1.88	0.02	2.59	0.17	0.44	0.00	
		25.14	18.72	32.96	8.38	5.31	9.50	
	ODNOTX	402	283	434	126	95	147	1,487
		431.93	283.38	422.75	115.52	91.92	141.51	11.92
		2.07	0.00	0.30	0.95	0.10	0.21	
		27.03	19.03	29.19	8.47	6.39	9.89	
	NOODTX	2,453	1,539	1,907	665	541	672	7,777
		2,259	1,482.10	2,211.00	604.18	480.72	740.10	62.35
		16.67	2.19	41.79	6.12	7.56	6.27	
		31.54	19.79	24.52	8.55	6.96	8.64	
Total		3,623	2,377	3,546	969	771	1,187	12,473
		29.05	19.06	28.43	7.77	6.18	9.52	100.00

* χ^2 (20, n = 16,655) = 278.74, p < 0.0001

Intervention Compliance

Intent-To-Treat Cohort

The frequency of three-year intervention compliance was determined for the ODA, ODAHRT, and ODHRT intervention groups. Patients were defined as being compliant with the intervention if they maintained an 80% or greater medication possession ratio (MPR) during the three-year observation period. For the intent-to-treat cohort, the ODA intervention group had the highest compliance (21.79%), followed by the ODAHRT (19.45%) and ODHRT (14.44%) intervention groups. A chi-square test for independence revealed that the relationship between intervention groups and intervention compliance was not independent $\chi^2 (2, n = 10,656) = 41.24, p < 0.0001$. Examination of observed cell frequencies vs. expected cell frequencies and cell chi-squares revealed significant differences for the distribution of patients who were compliant by intervention group. The ODA intervention group had a higher than expected cell frequency for compliance, whereas the ODHRT intervention group had a lower than expected cell frequency for compliance. Table 3.22 shows the frequency distribution of the cohort by intervention group and intervention compliance.

Table 3.22 ITT: Frequency distribution of the cohort by intervention group and intervention compliance

Frequency Expected Cell Chi-Square Row %		Compliant (80% MPR)		Total
		No	Yes	
Intervention Group	ODA	3,633	1,012	4,645
		3,729.60	915.4	43.59
		2.50	10.19	
		78.21	21.79	
	ODAHRT	3,537	854	4,391
		3,525.70	865.34	41.21
		0.04	0.15	
		80.55	19.45	
	ODHRT	1,386	234	1,620
		1,300.7	319.26	15.20
		5.59	22.77	
		85.56	14.44	
Total		8,556	2,100	10,656
		80.29	19.71	100.00

* χ^2 (2, n = 10,656) = 41.24, p < 0.0001

To further examine the extent of compliance for the three active intervention groups, frequency distributions were performed for each active intervention group by intervention compliance for the intent-to-treat cohort only. The frequency distribution of intervention compliance for the ODAHRT intervention group reflects intervention compliance with alendronate only, since the intervention inclusion criteria for ODAHRT intervention group did not require an index-prescription date for the HRT component. The majority of patients in each intervention group had medication possession ratios < 50% (ODA = 64.76%, ODHRT = 67.78%, and ODAHRT = 62.10%). Tables 3.23 to 3.25 show the frequency distributions of intervention compliance for the ODA, ODHRT, and ODAHRT intervention groups, respectively.

Table 3.23 ITT: Frequency distribution of the ODA intervention group by intervention compliance

% MPR	Frequency N = Patients	Percent	Cumulative Frequency	Cumulative Percent
0 to <10	784	16.89	784	16.89
10 to <20	544	11.72	1328	28.60
20 to <30	472	10.17	1800	38.77
30 to <40	626	13.48	2426	52.25
40 to <50	581	12.51	3007	64.76
50 to <60	254	5.47	3261	70.23
60 to <70	178	3.83	3439	74.07
70 to <80	192	4.14	3631	78.20
80 to <90	183	3.94	3814	82.15
> 90	829	17.85	4643	100.00

Table 3.24 ITT: Frequency distribution of the ODHRT intervention group by intervention compliance

% MPR	Frequency N = Patients	Percent	Cumulative Frequency	Cumulative Percent
0 to <10	299	18.46	299	18.46
10 to <20	179	11.05	478	29.51
20 to <30	169	10.43	647	39.94
30 to <40	242	14.94	889	54.88
40 to <50	209	12.90	1098	67.78
50 to <60	114	7.04	1212	74.81
60 to <70	99	6.11	1311	80.93
70 to <80	75	4.63	1386	85.56
80 to <90	76	4.69	1462	90.25
> 90	158	9.75	1620	100.00

Table 3.25 ITT: Frequency distribution of the ODAHRT intervention group by compliance

%MPR	Frequency N = Patients	Percent	Cumulative Frequency	Cumulative Percent
0 to <10	516	11.75	516	11.75
10 to <20	468	10.66	984	22.41
20 to <30	505	11.50	1489	33.91
30 to <40	649	14.78	2138	48.69
40 to <50	589	13.41	2727	62.10
50 to <60	249	5.67	2976	67.78
60 to <70	159	3.62	3135	71.40
70 to <80	149	3.39	3284	74.79
80 to <90	195	4.44	3479	79.23
> 90	912	20.77	4391	100.00

Non Intent-To-Treat Cohort

For the non intent-to-treat cohort, the ODA intervention group (22.81%) also had the highest compliance, followed by the ODAHRT (20.44%) and ODHRT (15.56%) intervention groups. A chi-square test for independence revealed that the relationship between intervention groups and intervention compliance was not independent $\chi^2 (2, n = 8,696) = 27.15, p < 0.0001$. Examination of observed cell frequencies vs. expected cell frequencies and cell chi-squares revealed the same significant differences for the distribution of patients who were compliant by intervention group that was observed in the intent-to-treat cohort for the non intent-to-treat cohort. Table 3.26 shows the frequency distribution of the cohort by intervention group and intervention compliance.

Table 3.26 Non-ITT: Frequency distribution of the cohort by intervention group and intervention compliance

Frequency Expected Cell Chi-Square Row %		Compliant (80% MPR)		Total
		No	Yes	
Intervention Group	ODA	2,968	877	3,845
		3,041.60	803.40	44.22
		1.78	6.74	
		43.15	22.81	
	ODAHRT	3,021	776	3,797
		3,003.60	793.37	43.66
		.10	0.38	
		79.56	20.44	
	ODHRT	890	164	1,054
		833.77	220.23	12.12
		3.79	14.36	
		84.44	15.56	
Total		6,879	1,817	8,696
		79.11	20.89	100.00

* χ^2 (2, n = 8,696) = 27.15, p < .0001

OBJECTIVE 1

The purpose of this objective was to assess the epidemiology of osteoporotic fracture in the study population. In the first part, the simple (unadjusted for covariates) three-year cumulative incidence and relative risk of an osteoporotic fracture was determined for the cohort as a whole and by intervention group. In the second part, the simple three-year cumulative incidence and relative risk of an osteoporotic fracture was determined for each risk factor. As previously discussed, two analyses were performed, one using an intent-to-treat study design and another using a non intent-to-treat study design.

Cumulative Incidence and Relative Risk of Osteoporotic Fracture for the Cohort and Intervention Groups

Intent-To-Treat Cohort

In the intent-to-treat cohort, 49,851 patients were at risk for osteoporotic fracture during the observation period. The three-year cumulative incidence of any osteoporotic fracture for the cohort was 2.48% (6.1% in patients with an osteoporosis diagnosis; 0.40% in patients without an osteoporosis diagnosis). Examination of the three-year cumulative incidence by fracture type revealed that vertebral fracture had the highest cumulative incidence 0.98%, followed by wrist (0.87%) and hip (0.64%).

Using the ODNOTX intervention group as the reference intervention group for the other intervention groups, the relative risk of osteoporotic fracture was calculated in addition to the three-year cumulative incidence for each intervention group. With few exceptions (hip), the ODA intervention group had a higher relative risk of osteoporotic fracture and for each specific type of osteoporotic fracture and the ODAHRT, ODHRT,

and NOODTX groups had a lower relative risk for osteoporotic fracture and for each specific type of osteoporotic fracture when compared to the ODNOTX intervention group. Among the active intervention groups, the ODHRT intervention group had the lowest relative risk for hip and wrist fracture, whereas the ODAHRT intervention group had the lowest relative risk for vertebral fracture. Table 3.27 shows the three-year cumulative incidence and relative risk of fracture for the cohort and intervention groups.

Table 3.27 ITT: Three-year cumulative incidence and relative risk of fracture for cohort and intervention groups

Intervention Group	Fracture Type	Fractures	Population at Risk (N)	Incidence per 100	Relative Risk
ODA	Hip	82	4,645	1.77	0.91
	Vertebral	114	4,645	2.45	1.04
	Wrist	136	4,645	2.93	1.27
	Total	332	4,645	7.15	1.08
ODAHRT	Hip	51	4,391	1.16	0.60
	Vertebral	64	4,391	1.46	0.62
	Wrist	84	4,391	1.91	0.83
	Total	199	4,391	4.53	0.69
ODHRT	Hip	15	1,620	0.93	0.48
	Vertebral	37	1,620	2.28	0.97
	Wrist	29	1,620	1.79	0.78
	Total	81	1,620	5.00	0.76
ODNOTX	Hip	147	7,568	1.94	
	Vertebral	179	7,568	2.37	
	Wrist	174	7,568	2.30	
	Total	500	7,568	6.61	
NOODTX	Hip	23	31,627	0.07	0.04
	Vertebral	94	31,627	0.30	0.13
	Wrist	9	31,627	0.03	0.01
	Total	126	31,627	0.40	0.06
Cohort	Hip	318	49,851	0.64	
	Vertebral	488	49,851	0.98	
	Wrist	432	49,851	0.87	
	Total	1,238	49,851	2.48	

* Reference group: ODNOTX

Non Intent-To-Treat Cohort

In the non intent-to-treat cohort, 38,283 patients were at risk for osteoporotic fracture during the observation period. The three-year cumulative incidence of osteoporotic fracture for the cohort was 1.93% (5.2% in patients with an osteoporosis diagnosis; 0.24% in patients without an osteoporosis diagnosis). In contrast to the intent-

to-treat cohort, wrist fracture had the highest cumulative incidence 0.74%, followed by vertebral (0.62%) and hip (0.56%).

As observed in the intent-to-treat cohort, the ODA intervention group had a higher relative risk of osteoporotic fracture and the ODAHRT, ODHRT, and NOODTX groups had a lower relative risk for osteoporotic fracture compared to the ODNOTX intervention group. Also as observed in the intent-to-treat cohort, among the active intervention groups, the ODHRT intervention group had the lowest relative risk for hip and wrist fracture, whereas the ODAHRT intervention group had the lowest relative risk for vertebral fracture. Table 3.28 shows the three-year cumulative incidence and relative risk of fracture for the cohort and intervention groups.

Table 3.28 Non- ITT: Three-year incidence and relative risk of fracture for cohort and intervention groups

Intervention Group	Fracture Type	Fractures	Population at Risk (N)	Incidence per 100	Relative Risk
ODA	Hip	68	3,845	1.77	0.90
	Vertebral	72	3,845	1.87	1.15
	Wrist	97	3,845	2.52	1.21
	Total	237	3,845	6.16	1.09
ODAHRT	Hip	45	3,797	1.19	0.60
	Vertebral	36	3,797	0.95	0.58
	Wrist	76	3,797	2.00	0.96
	Total	157	3,797	4.13	0.73
ODHRT	Hip	5	1,054	0.47	0.24
	Vertebral	15	1,054	1.42	0.88
	Wrist	18	1,054	1.71	0.82
	Total	38	1,054	3.61	0.63
ODNOTX	Hip	85	4,313	1.97	
	Vertebral	70	4,313	1.62	
	Wrist	90	4,313	2.09	
	Total	245	4,313	5.68	
NOODTX	Hip	12	25,274	0.05	0.02
	Vertebral	45	25,274	0.18	0.11
	Wrist	3	25,274	0.01	0.01
	Total	60	25,274	0.24	0.04
Cohort	Hip	215	38,283	0.56	
	Vertebral	238	38,283	0.62	
	Wrist	284	38,283	0.74	
	Total	737	38,283	1.93	

* Reference group: ODNOTX

Cumulative Incidence and Relative Risk of Osteoporotic Fracture by Risk Factor

Intent-To-Treat Cohort

For the intent-to-treat cohort, the cumulative incidence and relative risk of osteoporotic fracture was determined for each risk factor by first determining the incidence of osteoporotic fracture in the risk factor exposed and non-exposed populations, then dividing the incidence of the risk factor exposed population by the

incidence of the risk factor non-exposed population. The exception to this methodology was for the risk factor age, where age was categorized by 5-year intervals. For this risk factor, the first age category (50-54) served as the reference category.

In the intent-to-treat cohort, literature reports of an increased risk of osteoporotic fracture were substantiated for risk factors: age, osteoporosis diagnosis, previous osteoporotic fracture, and oral corticosteroid use. The relative risk of fracture increased with each successive increase in age-category, except in the 65-69 age-category, with the relative risk of osteoporotic fracture over 8-fold higher in the ≥ 85 age-category. A diagnosis of osteoporosis was shown to substantially increase the risk of osteoporotic fracture (RR = 15.32). Similarly, a prior osteoporotic fracture increased risk of a subsequent fracture over 11-fold. The relative risk of an osteoporotic fracture associated with corticosteroid use and statin use was examined two different ways: the first examined the relative risk regardless of dose and duration of exposure; the second considered dose and duration of exposure. Exposure to oral corticosteroids, regardless of dose and duration, increased the risk of fracture by 36%. Examination of oral corticosteroid dose and duration categories revealed that, in general, the relative risk of osteoporotic fracture substantially increased when the duration of exposure exceeded one-year at all doses. Evidence supporting a dose-response relationship was inconsistent. Statin use was found to have a protective effect at both low and high doses, more so when duration of exposure was less than two years. Here again, evidence supporting a dose-response relationship was weak. Intervention compliance was shown to be protective.

Table 3.29 ITT: Three-year incidence and relative risk of fracture for the cohort by risk factor

Risk Factor	Fractures	Population at Risk (N)	Incidence per 100	Relative Risk
Age Category				
50-54	96	9,360	1.03	
55-59	183	9,452	1.94	1.89
60-64	332	13,121	2.53	2.47
65-69	155	6,828	2.27	2.21
70-74	150	4,523	3.32	3.23
75-79	160	3,965	4.04	3.93
80-84	99	1,732	5.72	5.57
85 Plus	73	870	8.39	8.18
Osteoporosis Diagnosis				
Exposed	1,112	18,224	6.10	15.32
Non-exposed	126	31,627	0.40	
Previous Fracture				
Exposed	136	549	24.77	11.08
Non-exposed	1,102	49,302	2.24	
Corticosteroid Use				
Exposed	309	9,797	3.15	1.36
Non-exposed	929	40,054	2.32	
Corticosteroid Use (Dose; Duration)				
< 5mg; ≤ 180 days	6	494	1.21	0.52
< 5mg; > 180 ≤ 365 days	0	38	0.00	0.00
< 5mg; > 365 days	37	429	8.62	3.72
≥ 5 ≤ 10mg; ≤ 180 days	44	1,680	2.62	1.13
≥ 5 ≤ 10mg; > 180 ≤ 365 days	3	225	1.33	0.57
≥ 5 ≤ 10mg; > 365 days	47	712	6.60	2.85
> 10 ≤ 20mg; ≤ 180 days	44	1,976	2.23	0.96
> 10 ≤ 20mg; > 180 ≤ 365 days	8	195	4.10	1.77
> 10 ≤ 20mg; > 365 days	27	300	9.00	3.88
> 20mg; ≤ 180 days	83	3,587	2.31	1.00
> 20mg; > 180 ≤ 365 days	8	114	7.02	3.03
> 20mg; > 365 days	2	47	4.26	1.83

* Reference category for age was the 50-54 age-category

* Reference category for all others was the non-exposed

Table 3.29 ITT: Three-year incidence and relative risk of fracture for the cohort by risk factor (cont'd)

Risk Factor	Fractures	Population at Risk (N)	Incidence per 100	Relative Risk
Statin Use				
Exposed	308	16,655	1.85	0.66
Not Exposed	930	33,196	2.80	
Statin Use (Dose; Duration)				
Low; ≤ 1 year	60	4,827	1.24	0.44
Low; $> 1 \leq 2$ years	58	3,238	1.79	0.64
Low; > 2 years	114	4,598	2.48	0.88
High; ≤ 1 year	14	1,316	1.06	0.38
High; $> 1 \leq 2$ years	19	1,103	1.72	0.61
High; > 2 years	43	1,573	2.73	0.98
Intervention Compliance				
ODA				
Exposed	59	1,012	5.83	0.78
Not Exposed	273	3,633	7.51	
ODHRT				
Exposed	27	854	3.16	0.65
Not Exposed	172	3,537	4.86	
ODAHRT				
Exposed	9	234	3.85	0.74
Not Exposed	72	1,386	5.20	

* Reference category was the non-exposed

Non Intent-To-Treat Cohort

Overall, the relative risks associated with the risk factors in the non intent-to-treat cohort paralleled those in the intent-to-treat cohort. However, three discrepancies were found. First, the relative risk associated with a diagnosis of osteoporosis decreased from 15.32 for the intent-to-treat cohort to 10.55 for the non intent-to-treat cohort. Second, the relative risk associated with previous osteoporotic fracture increased from 11.08 in the intent-to-treat cohort to 21.92 in the non intent-to-treat cohort. Lastly, exposure to high dose statin for > 2 years was no longer found to be protective. Table 3.30 shows the three-year cumulative incidence and relative risk of fracture for the cohort by risk factor.

Table 3.30 Non-ITT: Three-year incidence and relative risk of fracture for the cohort by risk factor

Risk Factor	Fractures	Population at Risk (N)	Incidence per 100	Relative Risk
Age Category				
50-54	58	7,044	0.82	
55-59	101	7,183	1.41	1.71
60-64	173	9,659	1.79	2.18
65-69	96	5390	1.78	2.16
70-74	98	3,636	2.70	3.27
75-79	107	3,194	3.35	4.07
80-84	56	1,418	3.95	4.80
85 Plus	48	759	6.32	7.68
Osteoporosis Diagnosis				
Exposed	72	389	18.51	10.55
Not Exposed	665	37,894	1.75	
Previous Fracture				
Exposed	677	13,009	5.20	21.92
Not Exposed	60	25,274	0.24	
Corticosteroid Use				
Exposed	180	7,193	2.50	1.40
Not Exposed	557	31,090	1.79	
Corticosteroid Use (Dose; Duration)				
< 5mg; ≤ 180 days	3	363	0.83	0.46
< 5mg; > 180 ≤ 365 days	0	27	0.00	0.00
< 5mg; > 365 days	22	293	7.51	4.19
≥ 5 ≤ 10mg; ≤ 180 days	33	1,247	2.65	1.48
≥ 5 ≤ 10mg; > 180 ≤ 365 days	1	159	0.63	0.35
≥ 5 ≤ 10mg; > 365 days	22	485	4.54	2.53
> 10 ≤ 20mg; ≤ 180 days	26	1,456	1.79	1.00
> 10 ≤ 20mg; > 180 ≤ 365 days	4	145	2.76	1.54
> 10 ≤ 20mg; > 365 days	14	213	6.57	3.67
> 20mg; ≤ 180 days	51	2,691	1.90	1.06
> 20mg; > 180 ≤ 365 days	3	79	3.80	2.12
> 20mg; > 365 days	1	35	2.86	1.59

* Reference category for age was the 50-54 age-category

* Reference category for all others was the non-exposed

Table 3.30 Non-ITT: Three-year incidence and relative risk of fracture for the cohort by risk factor (cont'd)

Risk Factor	Fractures	Population at Risk (N)	Incidence per 100	Relative Risk
Statin Use				
Exposed	189	12,473	1.52	0.71
Not Exposed	548	25,810	2.12	
Statin Use (Dose; Duration)				
Low; ≤ 1 year	36	3,623	0.99	0.47
Low; $> 1 \leq 2$ years	32	2,377	1.35	0.63
Low; > 2 years	73	3,546	2.06	0.97
High; ≤ 1 year	9	969	0.93	0.44
High; $> 1 \leq 2$ years	10	771	1.30	0.61
High; > 2 years	29	1,187	2.44	1.15
Intervention Compliance				
ODA				
Exposed	43	877	4.90	0.75
Not Exposed	194	2,968	6.54	
ODAHRT				
Exposed	24	776	3.09	0.70
Not Exposed	133	3,021	4.40	
ODHRT				
Exposed	5	164	3.05	0.82
Not Exposed	33	890	3.71	

* Reference category was the non-exposed

OBJECTIVES 2 AND 3

Objective 1 determined the incidence and unadjusted relative risk of osteoporotic fracture for the cohort, each intervention group, and for the risk factors and covariates. The purpose of objectives 2 and 3 were to determine the effectiveness of the interventions in the prevention of osteoporotic fracture (objective 2) and to determine the significance of the study's risk factors and other covariates in the prediction of osteoporotic fracture events (objective 3), while controlling for exposure to risk factors. A series of logistic regression analyses was performed to accomplish both of these objectives. The retrospective cohort design used for objectives two and three is shown in Figure 3.1.

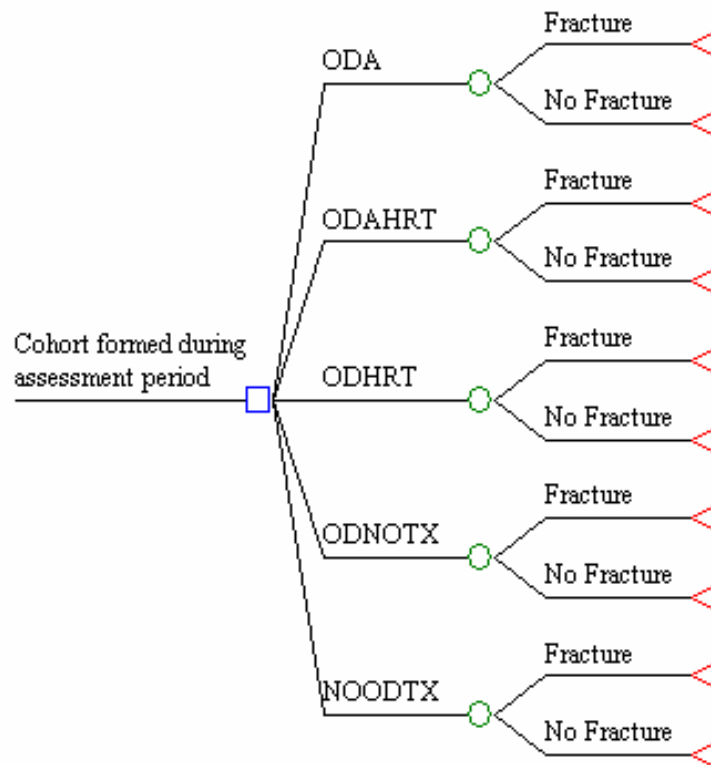


Figure 3.1 Retrospective Cohort Study Design

For objectives 2 and 3, the cohort was followed for the occurrence of any type of osteoporotic fracture event as well as for the occurrence of the specific types of osteoporotic fracture events (hip, vertebral, and wrist). Data from the cohort were analyzed to compare the risk of fracture between the intervention groups. Exposure to treatment intervention was determined, as previously described, using an intent-to-treat design (exposure measured at the onset of the observation period) and a non intent-to-treat design (exposure measured throughout the observation period).

Two series of logistic regression analyses were performed for objectives 2 and 3. The first series of logistic regression analyses, which were broader in scope, examined the risk of fracture for all five intervention groups (ODA, ODAHRT, ODHRT, ODNOTX, and NOODTX). Inclusion of all five intervention groups provided the ability to examine the increased risk of osteoporotic fracture associated with a diagnosis of osteoporosis. The first series of logistic regression analyses also explored the significance of all the risk factors and covariates; the primary purpose of which was to identify a set of more clinically relevant risk factors.

The second series of logistic regression analyses were more clinically focused. In this series of logistic regression analyses, the NOODTX intervention group was removed from the analyses, thus allowing a more focused analysis of the effectiveness of the active intervention groups (ODA, ODAHRT, and ODHRT) with the comparator intervention group (ODNOTX). In addition, given the results of the previous analyses, a decision was made to treat the risk factor age as a continuous variable instead of as a

categorical variable and to only assess the risk of osteoporotic fracture associated with long-term corticosteroid use (length of oral corticosteroid use > 1-year, for all doses).

In both the first series and second series of logistic regression analyses, four separate logistic regressions were performed, one for each type of fracture (any fracture, hip fracture, vertebral fracture, and wrist fracture), to determine the risk of fracture (intervention effectiveness) for each intervention group. For both the first and second series of logistic regression analyses, the significance of the risk factors and other covariates in the predication of osteoporotic fracture was determined from the output of the logistic regression analysis for any fracture. While both the treatment categories and covariates of interest were included in each regression analysis, the results of the treatment effects (objective 2 results) are described in separate tables from the covariate results (objective 3 results). The results from the first series (FS) of logistic regressions for intervention effectiveness and risk factor significance will be presented first for the intent-to-treat cohort and will be followed by the results for the non intent-to-treat cohort. The results from the second series (SS) of logistic regression analyses are presented last and will follow the same order as the first.

First Series of Logistic Regression Analyses

Intervention Effectiveness (Intent-To-Treat Cohort)

The binary logit regression model for the intent-to-treat cohort showed that the ODAHRT and NOODTX intervention groups had a significantly lower risk of experiencing an osteoporotic fracture event compared to the ODNOTX group (adjusted odds ratio (OR) = 0.702, 95% Wald Confidence Limits (CI) = 0.579 to 0.851, $p = 0.0003$;

OR = 0.065, 95% CI = 0.053 to 0.080, respectively). The ODAHRT and NOODTX intervention groups also had a significantly lower risk of experiencing a hip or vertebral osteoporotic fracture event compared to the ODNOTX intervention group (hip: OR = 0.657, 95% CI = 0.463 to 0.934, $p = 0.0192$; OR = 0.039, 95% CI = 0.025 to 0.061, $p < 0.0001$, respectively; vertebral: OR = 0.576, 95% CI = 0.416 to 0.797, $p = 0.0009$; OR = 0.140, 95% CI = 0.108 to 0.182, $p < 0.0001$, respectively). Only the NOODTX intervention group was shown to have a statistically significant lower risk of wrist fracture when compared to the ODNOTX intervention group (OR = 0.013, 95% CI = 0.007 to 0.025, $p = < 0.0001$). Table 3.31 shows the logistic regression intervention effectiveness parameter estimates.

Risk Factor Significance (Intent-To-Treat Cohort)

Risk factors: age, previous osteoporotic fracture, and oral corticosteroid use were shown to significantly increase the risk of osteoporotic fracture, whereas ODAHRT intervention compliance and statin use were shown to significantly decrease the risk of osteoporotic fracture. Using age-category 50 to 54 as the reference age-category, the risk of experiencing an osteoporotic fracture increased significantly with each successive increase in age-category (age-category 55 to 59: OR = 1.412, 95% CI = 1.082 to 1.843, $p = 0.0112$; age-category 60 to 64: OR = 1.601, 95% CI = 1.252 to 2.048, $p = 0.0002$; age-category 65 to 69: OR = 1.898, 95% CI = 1.435 to 2.512, $p < 0.0001$; age-category 70 to 74: OR = 2.713, 95% CI = 2.042 to 3.604, $p < 0.0001$; age-category 75 to 79: OR = 3.108, 95% CI = 2.349 to 4.112, $p < 0.0001$; age-category 80 to 84: OR = 4.730, 95% CI = 3.456 to 6.474, $p < 0.0001$; age-category ≥ 85 : OR = 6.194, 95% CI = 4.307 to 8.910, p

< 0.0001). Likewise, a previous osteoporotic fracture was shown to significantly increase the risk of a subsequent osteoporotic fracture (OR = 4.229, 95% CI = 3.358 to 5.326, $p < 0.0001$).

Evidence supporting an increased risk of osteoporotic fracture relative to oral corticosteroid dose and duration use was not as conclusive. Only corticosteroid dose/duration categories <5mg/>365 days and >10≤20mg/>365 days were found to significantly increase the risk of osteoporotic fracture (corticosteroid dose/duration category <5mg/>365 days: OR = 1.674, 95% CI = 1.119 to 2.503, $p = 0.0122$; corticosteroid dose/duration category: >10≤20mg/>365 days: OR = 2.153, 95% CI = 1.359 to 3.413, $p = 0.0011$). Although not statistically significant, corticosteroid dose/duration categories ≥5≤10mg/>365 days and >20mg/>180≤365 days approached the level of statistical significance. The parameter estimate for corticosteroid dose/duration category <5mg/>180≤365 days is probably erroneous due to small sample size and no fracture events.

Those patients who were compliant in the ODAHRT intervention group were shown to have a minimal additional protective effect when compared to the overall protective effect for the ODAHRT intervention group (OR = 0.616, 95% CI = 0.394 to 0.963, $p = 0.0336$ versus OR = 0.702, 95% CI = 0.579 to 0.851, $p = 0.0003$, respectively). Statin use was shown to have a statistically significant protective effective for osteoporotic fracture for low dose statin for each level of duration (statin dose/duration category: low/≤1 year: OR = 0.417, 95% CI = 0.313 to 0.556, $p < 0.0001$; statin dose/duration category: low/>1≤2 years: OR = 0.626, 95% CI = 0.471 to 0.834, $p <$

0.0013; statin dose/duration category: low/>2 years: OR = 0.653, 95% CI = 0.526 to 0.811, p = 0.0001) and for high dose statin dose/duration category - high/≤ 1year (OR = 0.418, CI = 0.239 to 0.731, p = 0.0022). Table 3.32 shows the logistic regression risk factor parameter estimates.

Table 3.31 FS ITT: Logistic regression intervention effectiveness parameter estimates

Fracture Type Intervention Group	Estimate	Pr > ChiSq	Adjusted Odds Ratio		
			Point Estimate	95% Wald Confidence Limits	
Any Fracture					
ODA	-0.0893	0.3109	0.915	0.770	1.087
ODAHRT	-0.3537	0.0003	0.702	0.579	0.851
ODHRT	-0.1405	0.3185	0.869	0.659	1.145
NOODTX	-2.7299	< 0.0001	0.065	0.053	0.080
Hip					
ODA	-0.2710	0.0858	0.763	0.560	1.039
ODAHRT	-0.4195	0.0192	0.657	0.463	0.934
ODHRT	-0.5186	0.0913	0.595	0.326	1.087
NOODTX	-3.2398	< 0.0001	0.039	0.025	0.061
Vertebral					
ODA	-0.1387	0.3180	0.871	0.663	1.143
ODAHRT	-0.5515	0.0009	0.576	0.416	0.797
ODHRT	0.0966	0.6355	1.101	0.739	1.642
NOODTX	-1.9667	< 0.0001	0.140	0.108	0.182
Wrist					
ODA	0.0972	0.4665	1.102	0.848	1.431
ODAHRT	-0.1950	0.1877	0.823	0.616	1.100
ODHRT	-0.1522	0.4850	0.859	0.560	1.317
NOODTX	-4.3611	< 0.0001	0.013	0.007	0.025

* Bolded = p < 0.05

Table 3.32 FS ITT: Logistic regression risk factor parameter estimates

Parameter	Estimate	Pr > ChiSq	Adjusted Odds Ratio		
			Point Estimate	95% Wald Confidence Limits	
Age Category					
55 - 59	0.3448	0.0112	1.412	1.082	1.843
60 – 64	0.4708	0.0002	1.601	1.252	2.048
65 – 69	0.6410	< 0.0001	1.898	1.435	2.512
70 – 74	0.9980	< 0.0001	2.713	2.042	3.604
75 – 79	1.1339	< 0.0001	3.108	2.349	4.112
80 – 84	1.5540	< 0.0001	4.730	3.456	6.474
≥ 85	1.8236	< 0.0001	6.194	4.307	8.910
Intervention Compliance					
ODA 80% MPR	-0.3025	0.0636	0.739	0.537	1.017
ODHRT 80% MPR	-0.2645	0.4936	0.768	0.360	1.637
ODAHRT 80% MPR	-0.4851	0.0336	0.616	0.394	0.963
Corticosteroid Use					
<5mg; ≤180 days	-0.6829	0.1017	0.505	0.223	1.144
<5mg; >180≤365 days	-11.2078	0.9629	< 0.0001	< 0.0001	> 999.99
<5mg; >365 days	0.5150	0.0122	1.674	1.119	2.503
≥5≤10mg; ≤180 days	-0.0159	0.9265	0.984	0.702	1.380
≥5≤10mg; >180≤ 365 days	-0.7365	0.2108	0.479	0.151	1.517
≥5≤10mg; >365 days	0.3269	0.0671	1.387	0.977	1.967
>10≤ 20mg; ≤180 days	-0.0982	0.5531	0.906	0.655	1.254
>10≤ 20mg; >180≤365 days	0.3392	0.3664	1.404	0.673	2.930
>10≤ 20mg; >365 days	0.7671	0.0011	2.153	1.359	3.413
>20mg; ≤180 days	-0.0364	0.7679	0.964	0.757	1.228
>20mg; >180≤365 days	0.8104	0.0656	2.249	0.949	5.328
>20mg; >365 days	0.5337	0.4716	1.705	0.399	7.293
Statin Use					
Low; ≤1 year	-0.8743	< 0.0001	0.417	0.313	0.556
Low; >1≤ 2 years	-0.4679	0.0013	0.626	0.471	0.834
Low; >2 years	-0.4263	0.0001	0.653	0.526	0.811
High; ≤1 year	-0.8720	0.0022	0.418	0.239	0.731
High; >1≤ 2 years	-0.4481	0.0756	0.639	0.390	1.047
High; >2 years	-0.2917	0.1025	0.747	0.526	1.060
Previous Fracture					
Previous Fracture	1.4421	< 0.0001	4.229	3.358	5.326

* Bolded = p < 0.05

Intervention Effectiveness (Non Intent-To-Treat Cohort)

Comparison of the intervention effectiveness results of obtained for the non intent-to-treat cohort to the intent-to-treat cohort revealed two major differences. First, the ODAHRT intervention group was found only to have a statistically significant lower risk of vertebral fracture. Second, the ODHRT intervention group was found to have a statistically significant lower risk of hip fracture. Table 3.33 provides the intervention effectiveness parameter estimates for the non intent-to-treat cohort.

Table 3.33 FS Non-ITT: Logistic regression intervention effectiveness parameter estimates

Fracture Type Intervention Group	Estimate	Pr > ChiSq	Adjusted Odds Ratio		
			Point Estimate	95% Wald Confidence Limits	
Any Fracture					
ODA	-0.0106	0.9235	0.989	0.798	1.228
ODAHRT	-0.2160	0.0686	0.806	0.639	1.017
ODHRT	-0.1815	0.3615	0.834	0.565	1.232
NOODTX	-3.0712	< 0.0001	0.046	0.035	0.062
Hip					
ODA	-0.1605	0.3827	0.852	0.594	1.221
ODAHRT	-0.3015	0.1423	0.740	0.494	1.107
ODHRT	-1.3053	0.0281	0.271	0.085	0.869
NOODTX	-3.6087	< 0.0001	0.027	0.015	0.050
Vertebral					
ODA	0.0589	0.7570	1.061	0.730	1.540
ODAHRT	-0.5129	0.0263	0.599	0.381	0.941
ODHRT	0.2427	0.4209	1.275	0.706	2.302
NOODTX	-2.0718	< 0.0001	0.126	0.085	0.186
Wrist					
ODA	0.0756	0.6507	1.079	0.777	1.496
ODAHRT	-0.0395	0.8189	0.961	0.685	1.348
ODHRT	-0.0833	0.7700	0.920	0.527	1.608
NOODTX	-5.1456	< 0.0001	0.006	0.002	0.018

* Bolded = p < 0.05

Risk Factor Significance (Non Intent-To-Treat Cohort)

Comparison of risk factor significance results obtained for the non intent-to-treat cohort to the intent-to-treat cohort also revealed two major differences. First, the ODAHRT intervention compliance no longer afforded an additional statistically significant protective effect. Second, the corticosteroid dose/duration category $\geq 5 \leq 10 \text{mg}/>365$ days no longer had a statistically significant increased risk of osteoporotic fracture. Table 3.34 provides the logistic regression risk factor parameter estimates for the non intent-to-treat cohort.

Table 3.34 FS Non-ITT: Logistic regression risk factor parameter estimates

Parameter	Estimate	Pr > ChiSq	Adjusted Odds Ratio		
			Point Estimate	95% Wald Confidence Limits	
Age Category					
55 - 59	0.2472	0.1573	1.280	0.909	1.804
60 – 64	0.3784	0.0189	1.460	1.064	2.002
65 – 69	0.5009	0.0056	1.650	1.158	2.352
70 – 74	0.8533	< 0.0001	2.347	1.642	3.356
75 – 79	1.0518	< 0.0001	2.863	2.021	4.055
80 – 84	1.3157	< 0.0001	3.727	2.493	5.573
≥ 85	1.7342	< 0.0001	5.665	3.633	8.832
Intervention Compliance					
ODA 80% MPR	-0.2991	0.1091	0.741	0.514	1.069
ODHRT 80% MPR	-0.4004	0.4600	0.670	0.232	1.938
ODAHRT 80% MPR	-0.4112	0.0881	0.663	0.413	1.063
Corticosteroid Use					
<5mg; ≤180 days	-0.8495	0.1477	0.428	0.135	1.351
<5mg; >180≤365 days	-11.0835	0.9699	<0.001	<0.001	>999.999
<5mg; >365 days	0.5497	0.0364	1.733	1.036	2.899
≥5≤10mg; ≤180 days	0.1995	0.3154	1.221	0.827	1.802
≥5≤10mg; >180≤ 365 days	-1.3050	0.1961	0.271	0.037	1.961
≥5≤10mg; >365 days	0.0797	0.7498	1.083	0.663	1.768
>10≤ 20mg; ≤180 days	-0.0790	0.7082	0.924	0.611	1.397
>10≤ 20mg; >180≤365 days	0.1020	0.8448	1.107	0.399	3.076
>10≤ 20mg; >365 days	0.7400	0.0138	2.096	1.163	3.776
>20mg; ≤180 days	-0.0780	0.6234	0.925	0.678	1.263
>20mg; >180≤365 days	0.2589	0.7256	1.295	0.305	5.499
>20mg; >365 days	0.2098	0.8394	1.233	0.162	9.389
Statin Use					
Low; ≤1 year	-0.8817	< 0.0001	0.414	0.284	0.603
Low; >1≤ 2 years	-0.5093	0.0082	0.601	0.412	0.877
Low; >2 years	-0.4071	0.0032	0.666	0.508	0.872
High; ≤1 year	-0.8086	0.0258	0.445	0.219	0.907
High; >1≤ 2 years	-0.4239	0.2186	0.654	0.333	1.286
High; >2 years	-0.2782	0.2153	0.757	0.488	1.176
Previous Fracture					
Previous Fracture	1.2302	< 0.0001	3.422	2.527	4.634

* Bolded = p < 0.05

Second Series of Logistic Regression Analyses

The second series of logistic regression analyses involved only those intervention groups with a diagnosis of osteoporosis. The first series of regression analyses revealed that the risk of an osteoporotic fracture event increased with each successive increase in age-category. Therefore, a decision was made to simplify age from a categorical to a continuous variable, and thereby capture the ordinal influence of this covariate. The first series of regression analyses also suggested that possibly only long-term use of oral corticosteroids was associated with a statistically significant increased risk of osteoporotic fracture. Therefore, in the second series of logistic regression analyses, only long-term (length of oral corticosteroid use >1-year, for all doses) oral corticosteroid use was assessed as a risk factor.

A comparison of the logistic regression intervention effectiveness parameter estimates of the second series of logistic regression analyses to the first series for both the intent-to-treat cohort and non intent-to-treat cohort revealed no differences as to which intervention groups had a statistically significant decreased risk of osteoporotic fracture among the active intervention groups. Furthermore, there was little difference in the adjusted odds ratio point estimates.

Results from the second series of logistic regression risk factor parameter estimates for both the intent-to-treat and non intent-to-treat cohorts revealed that for each one-year increase in age there was a statistically significant increased risk of osteoporotic fracture (OR = 1.047, 95% CI = 1.039 to 1.055, $p < 0.0001$; OR = 1.047, 95% CI = 1.037 to 1.056, $p < 0.0001$, respectively). Results for both cohorts also showed that oral corticosteroid use for a duration of > 1-year was associated with a statistically significant increased risk of osteoporotic fracture (OR = 1.533, 95% CI = 1.220 to 1.977, $p = 0.0003$; OR = 1.379, 95% CI = 1.002 to 1.898, $p = 0.0488$, respectively). As for the other risk

factors and covariates, the results obtained for the second series of logistic regression risk factor parameter estimates paralleled those obtained for their respective cohorts in the first series of logistic regression analyses. Tables 3.35 to 3.38 show the results for the second series of logistic regressions.

Table 3.35 SS ITT: Logistic regression intervention effectiveness parameter estimates

Fracture Type Intervention Group	Estimate	Pr > ChiSq	Adjusted Odds Ratio		
			Point Estimate	95% Wald Confidence Limits	
Any Fracture					
ODA	-0.0810	0.3512	0.922	0.778	1.093
ODAHRT	-0.3594	0.0002	0.698	0.577	0.845
ODHRT	-0.1515	0.2819	0.859	0.652	1.132
Hip					
ODA	-0.2875	0.0632	0.750	0.554	1.016
ODAHRT	-0.4458	0.0117	0.640	0.453	0.906
ODHRT	-0.5148	0.0938	0.598	0.327	1.091
Vertebral					
ODA	-0.1211	0.3775	0.886	0.677	1.159
ODAHRT	-0.5444	0.0009	0.580	0.421	0.800
ODHRT	0.0893	0.6613	1.093	0.733	1.630
Wrist					
ODA	0.1412	0.2829	1.152	0.890	1.490
ODAHRT	-0.1702	0.2448	0.843	0.633	1.124
ODHRT	-0.1666	0.4442	0.847	0.552	1.297

* Bolded = $p < 0.05$

Table 3.36 SS ITT: Logistic regression risk factor parameter estimates

Parameter	Estimate	Pr > ChiSq	Adjusted Odds Ratio		
			Point Estimate	95% Wald Confidence Limits	
Age					
Age	0.0459	< 0.0001	1.047	1.039	1.055
Intervention Compliance					
ODA 80% MPR	-0.2966	0.0682	0.743	0.540	1.022
ODHRT 80% MPR	-0.2498	0.5173	0.779	0.366	1.659
ODAHRT 80% MPR	-0.4951	0.0300	0.610	0.390	0.953
Corticosteroid Use					
≤ 1-year	-0.0980	0.2822	0.907	0.758	1.084
≥ 1-year	0.4403	0.0003	1.553	1.220	1.977
Statin Use					
Low; ≤1 year	-0.8747	< 0.0001	0.417	0.307	0.566
Low; >1≤ 2 years	-0.4850	0.0018	0.616	0.454	0.834
Low; >2 years	-0.4339	0.0001	0.648	0.518	0.811
High; ≤1 year	-0.7507	0.0087	0.472	0.269	0.827
High; >1≤ 2 years	-0.4688	0.0814	0.626	0.369	1.060
High; >2 years	-0.3765	0.0504	0.686	0.471	1.001
Previous Fracture					
Previous Fracture	1.4536	< 0.0001	4.279	3.401	5.382

* Bolded = p < 0.05

Table 3.37 SS Non-ITT: Logistic regression intervention effectiveness parameter estimates

Fracture Type Intervention Group	Estimate	Pr > ChiSq	Adjusted Odds Ratio		
			Point Estimate	95% Wald Confidence Limits	
Any Fracture					
ODA	-0.0177	0.8702	0.982	0.794	1.215
ODAHRT	-0.2289	0.0509	0.795	0.632	1.001
ODHRT	-0.1803	0.3649	0.835	0.565	1.233
Hip					
ODA	-0.1695	0.3476	0.844	0.593	1.202
ODAHRT	-0.3129	0.1235	0.731	0.491	1.089
ODHRT	-1.2659	0.0333	0.282	0.088	0.905
Vertebral					
ODA	0.0569	0.7619	1.059	0.733	1.529
ODAHRT	-0.5239	0.0222	0.592	0.378	0.928
ODHRT	0.2390	0.4287	1.270	0.703	2.296
Wrist					
ODA	0.1032	0.5313	1.109	0.803	1.532
ODAHRT	-0.0201	0.9061	0.980	0.702	1.369
ODHRT	-0.1005	0.7237	0.904	0.518	1.579

* Bolded = $p < 0.05$

Table 3.38 SS Non-ITT: Logistic regression risk factor parameter estimates

Parameter	Estimate	Pr > ChiSq	Adjusted Odds Ratio		
			Point Estimate	95% Wald Confidence Limits	
Age					
Age	0.0455	< 0.0001	1.047	1.037	1.056
Intervention Compliance					
ODA 80% MPR	-0.2963	0.1116	0.744	0.516	1.071
ODHRT 80% MPR	-0.3697	0.4946	0.691	0.239	1.996
ODAHRT 80% MPR	-0.4167	0.0836	0.659	0.411	1.057
Corticosteroid Use					
≤ 1-year	-0.1105	0.3356	0.895	0.715	1.121
≥ 1-year	0.3214	0.0488	1.379	1.002	1.898
Statin Use					
Low; ≤1 year	-0.8917	< 0.0001	0.410	0.276	0.609
Low; >1≤ 2 years	-0.4669	0.0174	0.627	0.427	0.921
Low; >2 years	-0.4325	0.0023	0.649	0.492	0.857
High; ≤1 year	-0.7131	0.0500	0.490	0.240	1.000
High; >1≤ 2 years	-0.5904	0.1294	0.554	0.258	1.189
High; >2 years	-0.2792	0.2247	0.756	0.482	1.187
Previous Fracture					
Previous Fracture	1.2372	< 0.0001	3.446	2.548	4.660

* Bolded = p < 0.05

OBJECTIVE 4

Objective 2 determined the effectiveness of the interventions in the prevention of osteoporotic fracture, while controlling for exposure to risk factors using a logistic regression analysis. For this objective, a series of survival analyses were performed to compare the time to fracture for the intervention groups. There were two general goals of these analyses: 1) to describe the proportion of cases free of a fracture event at various points in time, and 2) to assess the relationship between survival time and a set of covariates to determine whether treatment differences exist after statistically controlling for the other covariates.

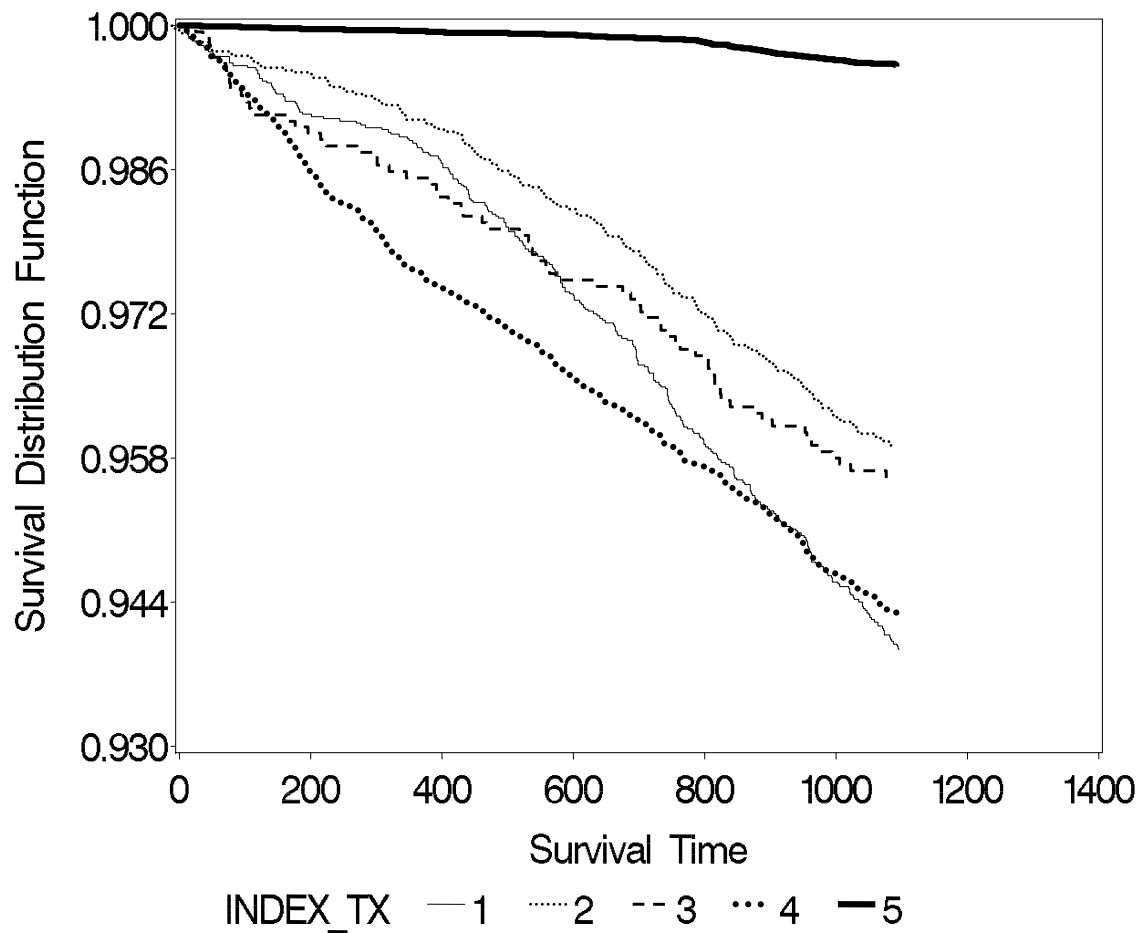
Kaplan-Meier Life Tables and Survival Plots

Intent-To-Treat Cohort

The Kaplan-Meier method of life tables was used to describe the proportion of cases free of a fracture event at various points in time. Life tables were constructed to describe the proportion of cases free of any fracture event, hip fracture event, vertebral fracture event, and wrist fracture event at various points in time. Given the lengthy output of the life tables, life tables with selected output at 6-month duration intervals were constructed. The dependent variable, days, was the number of days a case was free of a fracture event during the three-year observation period. Fracture event was the censoring variable that indicated whether a case was fracture-free at the end of the observation period. In addition, survival plots were constructed to provide a visual preliminary examination of the data.

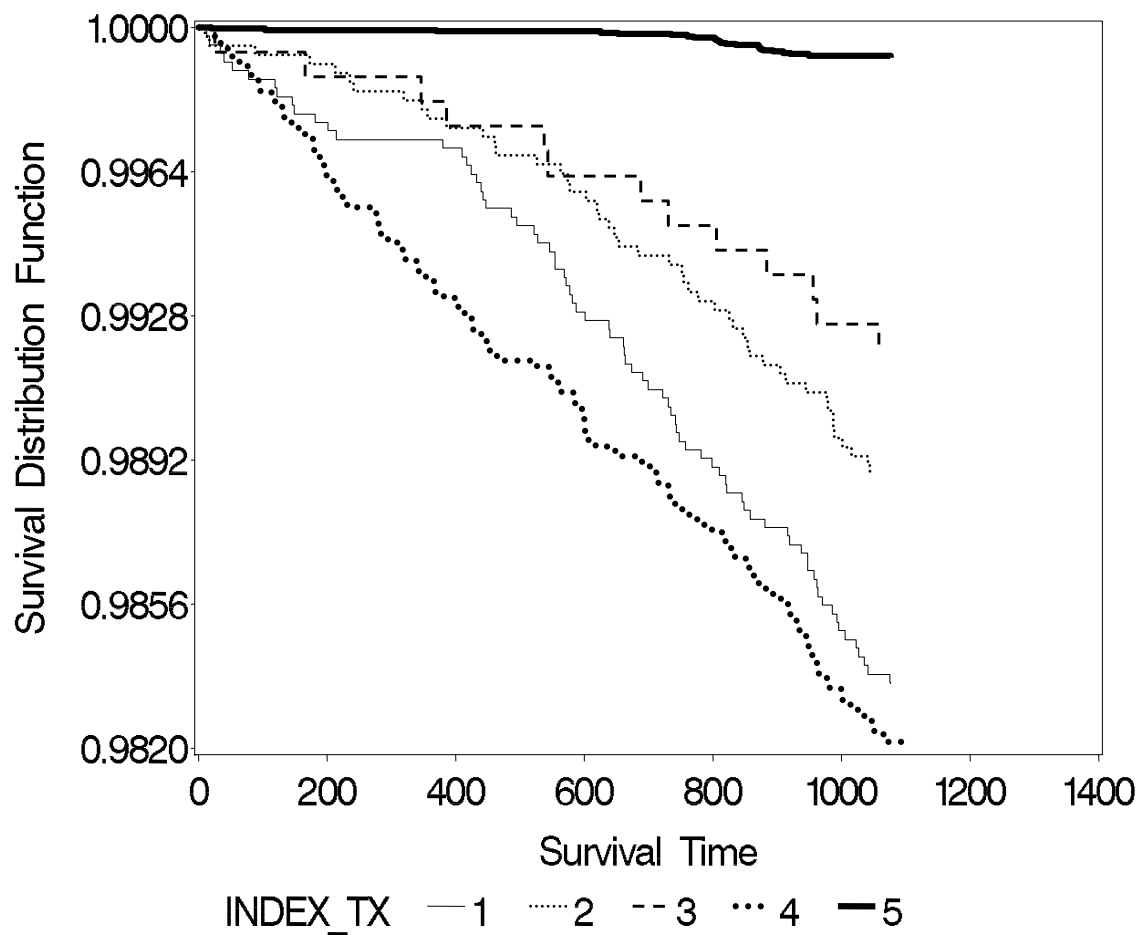
The results revealed that there were statistically significant differences in survival functions between the intervention groups for: any fracture event, hip fracture event, vertebral fracture event, and wrist fracture event ($p < 0.0001$). As expected, examination of the Kaplan-Meier estimates (survival) revealed that the NOODTX intervention group had the greatest probability that a patient would be fracture-free at each duration interval for any fracture and for each specific type of fracture. Among intervention groups with an existing osteoporosis diagnosis, the ODAHRT intervention group had the greatest probability that a patient would be fracture-free at each duration interval for any fracture and for vertebral fracture. For hip fracture, the ODAHRT intervention group had the greatest probability that a patient would be fracture-free for up to 1 ½ years. At 1 ½ years or more, the ODAHRT intervention group had the highest probability that a patient would be fracture-free. Similarly for wrist fracture, the ODAHRT intervention group had the greatest probability that a patient would be fracture-free up to two years. At two years or more, the ODAHRT intervention group had the highest probability that a patient would be fracture-free. Survival plots are presented in Figures 3.2 to 3.5 for: any fracture, hip fracture, vertebral fracture, and wrist fracture, respectively. Tables 3.39 to 3.42 show the Kaplan-Meier life tables for: any fracture, hip fracture, vertebral fracture, and wrist fracture, respectively.

Figure 3.2 ITT: Kaplan-Meier survival curve for any fracture



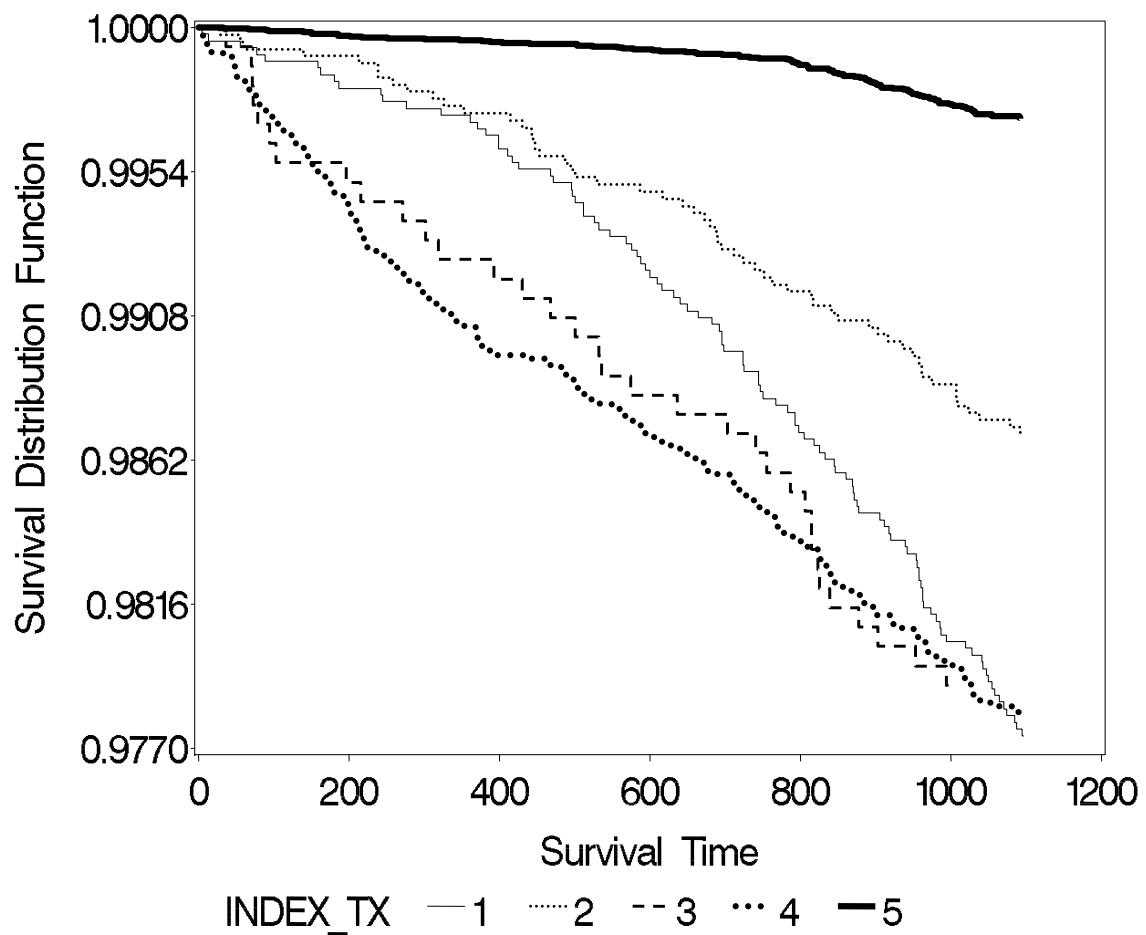
* Index_TX 1: ODA intervention group; Index_TX 2: ODAHRT intervention group;
 Index_TX 3: ODHRT intervention group; Index_TX 4: ODNOTX intervention group;
 Index_TX 5: NOODTX intervention group; Survival Time: Days

Figure 3.3 ITT: Kaplan-Meier survival curve for hip fracture



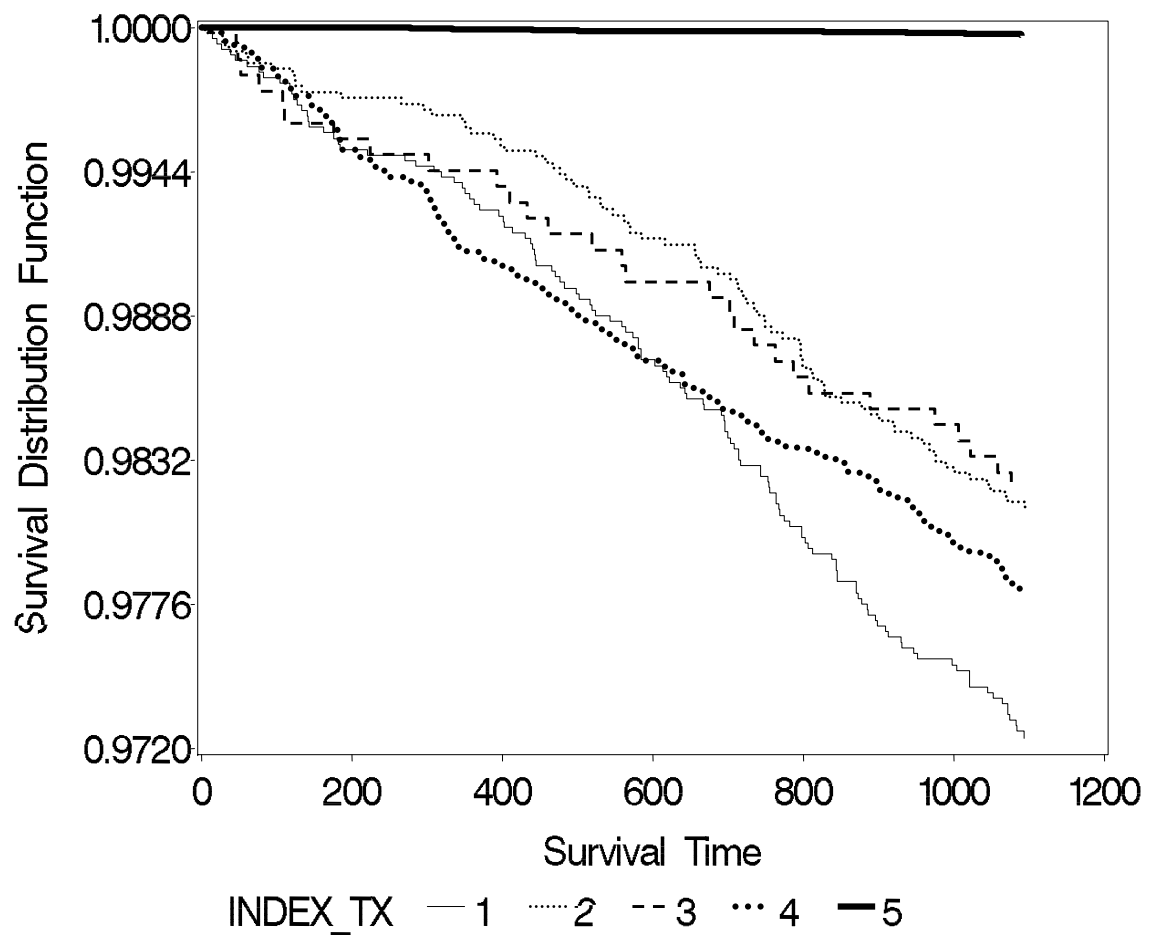
* Index_TX 1: ODA intervention group; Index_TX 2: ODAHRT intervention group;
 Index_TX 3: ODHRT intervention group; Index_TX 4: ODNOTX intervention group;
 Index_TX 5: NOODTX intervention group; Survival Time: Days

Figure 3.4 ITT: Kaplan-Meier survival curve for vertebral fracture



* Index_TX 1: ODA intervention group; Index_TX 2: ODAHRT intervention group;
 Index_TX 3: ODHRT intervention group; Index_TX 4: ODNOTX intervention group;
 Index_TX 5: NOODTX intervention group; Survival Time: Days

Figure 3.5 ITT: Kaplan-Meier survival curve for wrist fracture



* Index_TX 1: ODA intervention group; Index_TX 2: ODAHRT intervention group;
 Index_TX 3: ODHRT intervention group; Index_TX 4: ODNOTX intervention group;
 Index_TX 5: NOODTX intervention group; Survival Time: Days

Table 3.39 ITT: Kaplan-Meier Life Table for any fracture

Time Interval Intervention Group	Survival	Failure	Survival S.E.	Number Failed	Number Left
6- Month					
ODA	0.9922	0.00775	0.00129	36	4,609
ODAHRT	0.9954	0.00455	0.00102	20	4,371
ODHRT	0.9895	0.0105	0.00253	17	1,603
ODNOTX	0.9874	0.0126	0.00128	95	7,473
NOODTX	0.9997	0.000316	0.000100	10	31,617
1 - Year					
ODA	0.9879	0.0121	0.00160	56	4,589
ODAHRT	0.9907	0.00934	0.00145	41	4,350
ODHRT	0.9846	0.0154	0.00306	25	1,595
ODNOTX	0.9757	0.0243	0.00177	184	7,384
NOODTX	0.9994	0.000569	0.000134	18	31,609
1 ½ - Years					
ODA	0.9776	0.0224	0.00217	104	4,541
ODAHRT	0.9843	0.0157	0.00188	69	4,322
ODHRT	0.9765	0.0235	0.00376	38	1,582
ODNOTX	0.9686	0.0314	0.00201	238	7,330
NOODTX	0.9991	0.000854	0.000164	27	31,600
2 - Years					
ODA	0.9651	0.0349	0.00269	162	4,483
ODAHRT	0.9765	0.0235	0.00228	103	4,288
ODHRT	0.9710	0.0290	0.00417	47	1,573
ODNOTX	0.9602	0.0398	0.00225	301	7,267
NOODTX	0.9987	0.00126	0.000200	40	31,587
2 ½ - Years					
ODA	0.9522	0.0478	0.00313	222	4,423
ODAHRT	0.9672	0.0328	0.00269	144	4,247
ODHRT	0.9605	0.0395	0.00484	64	1,556
ODNOTX	0.9519	0.0481	0.00246	364	7,204
NOODTX	0.9972	0.00278	0.000296	88	31,539
3 - Years					
ODA	0.9395	0.0605	0.00350	281	4,364
ODAHRT	0.9592	0.0408	0.00298	179	4,212
ODHRT	0.9562	0.0438	0.00509	71	1,549
ODNOTX	0.9428	0.0572	0.00267	433	7,135
NOODTX	0.9962	0.00376	0.000344	119	31,508

Table 3.40 ITT: Kaplan-Meier Life Table for hip fracture

Time Interval Intervention Group	Survival	Failure	Survival S.E.	Number Failed	Number Left
6- Month					
ODA	0.9976	0.00237	0.000713	11	4,634
ODAHRT	0.9989	0.00114	0.000509	5	4,386
ODHRT	0.9981	0.00185	0.00107	3	1,617
ODNOTX	0.9968	0.00317	0.000646	24	7,544
NOODTX	0.9999	0.000095	0.000055	3	31,624
1 - Year					
ODA	0.9970	0.00301	0.000804	14	4,631
ODAHRT	0.9975	0.00251	0.000754	11	4,380
ODHRT	0.9975	0.00247	0.00123	4	1,616
ODNOTX	0.9935	0.00647	0.000922	49	7,519
NOODTX	0.9999	0.000095	0.000055	3	31,624
1 ½ - Years					
ODA	0.9944	0.00560	0.00109	26	4,619
ODAHRT	0.9964	0.00364	0.000909	16	4,375
ODHRT	0.9957	0.00432	0.00163	7	1,613
ODNOTX	0.9913	0.00872	0.00107	66	7,502
NOODTX	0.9999	0.000126	0.000063	4	31,623
2 - Years					
ODA	0.9905	0.00947	0.00142	44	4,601
ODAHRT	0.9941	0.00592	0.00116	26	4,365
ODHRT	0.9951	0.00494	0.00174	8	1,612
ODNOTX	0.9885	0.0115	0.00123	87	7,481
NOODTX	0.9997	0.000253	0.000089	8	31,619
2 ½ - Years					
ODA	0.9873	0.0127	0.00164	59	4,586
ODAHRT	0.9911	0.00888	0.00142	39	4,352
ODHRT	0.9932	0.00679	0.00204	11	1,609
ODNOTX	0.9856	0.0144	0.00137	109	7,459
NOODTX	0.9993	0.000664	0.000145	21	31,606
3 - Years					
ODA	0.9836	0.0164	0.00186	76	4,569
ODAHRT	0.9888	0.0112	0.00159	49	4,342
ODHRT	0.9920	0.00802	0.00222	13	1,607
ODNOTX	0.9820	0.0180	0.00153	136	7,432
NOODTX	0.9993	0.000727	0.000152	23	31,604

Table 3.41 ITT: Kaplan-Meier Life Table for vertebral fracture

Time Interval Intervention Group	Survival	Failure	Survival S.E.	Number Failed	Number Left
6- Month					
ODA	0.9983	0.00172	0.000608	8	4,637
ODAHRT	0.9989	0.00114	0.000509	5	4,386
ODHRT	0.9951	0.00494	0.00174	8	1,612
ODNOTX	0.9947	0.00529	0.000833	40	7,528
NOODTX	0.9997	0.000253	0.00089	8	31,619
1 - Year					
ODA	0.9968	0.00323	0.000832	15	4,630
ODAHRT	0.9970	0.00296	0.000820	13	4,378
ODHRT	0.9920	0.00802	0.00222	13	1,607
ODNOTX	0.9902	0.00978	0.00113	74	7,494
NOODTX	0.9996	0.000443	0.000118	14	31,613
1 ½ - Years					
ODA	0.9933	0.00667	0.00119	31	4,614
ODAHRT	0.9948	0.00524	0.00109	23	4,368
ODHRT	0.9883	0.0117	0.00267	19	1,601
ODNOTX	0.9878	0.0122	0.00126	92	7,476
NOODTX	0.9994	0.000632	0.000141	20	31,607
2 - Years					
ODA	0.9886	0.0114	0.00156	53	4,592
ODAHRT	0.9923	0.00774	0.00132	34	4,357
ODHRT	0.9864	0.0136	0.00288	22	1,598
ODNOTX	0.9849	0.0151	0.00140	114	7,454
NOODTX	0.9991	0.000949	0.000173	30	31,597
2 ½ - Years					
ODA	0.9841	0.0159	0.00184	74	4,571
ODAHRT	0.9900	0.0100	0.00150	44	4,347
ODHRT	0.9796	0.0204	0.00351	33	1,587
ODNOTX	0.9811	0.0189	0.00157	143	7,425
NOODTX	0.9980	0.00196	0.000249	62	31,565
3 - Years					
ODA	0.9774	0.0226	0.00218	105	4,540
ODAHRT	0.9870	0.0130	0.00171	57	4,334
ODHRT	0.9790	0.210	0.00356	34	1,586
ODNOTX	0.9781	0.0219	0.00168	166	7,402
NOODTX	0.9972	0.00281	0.000298	89	31,538

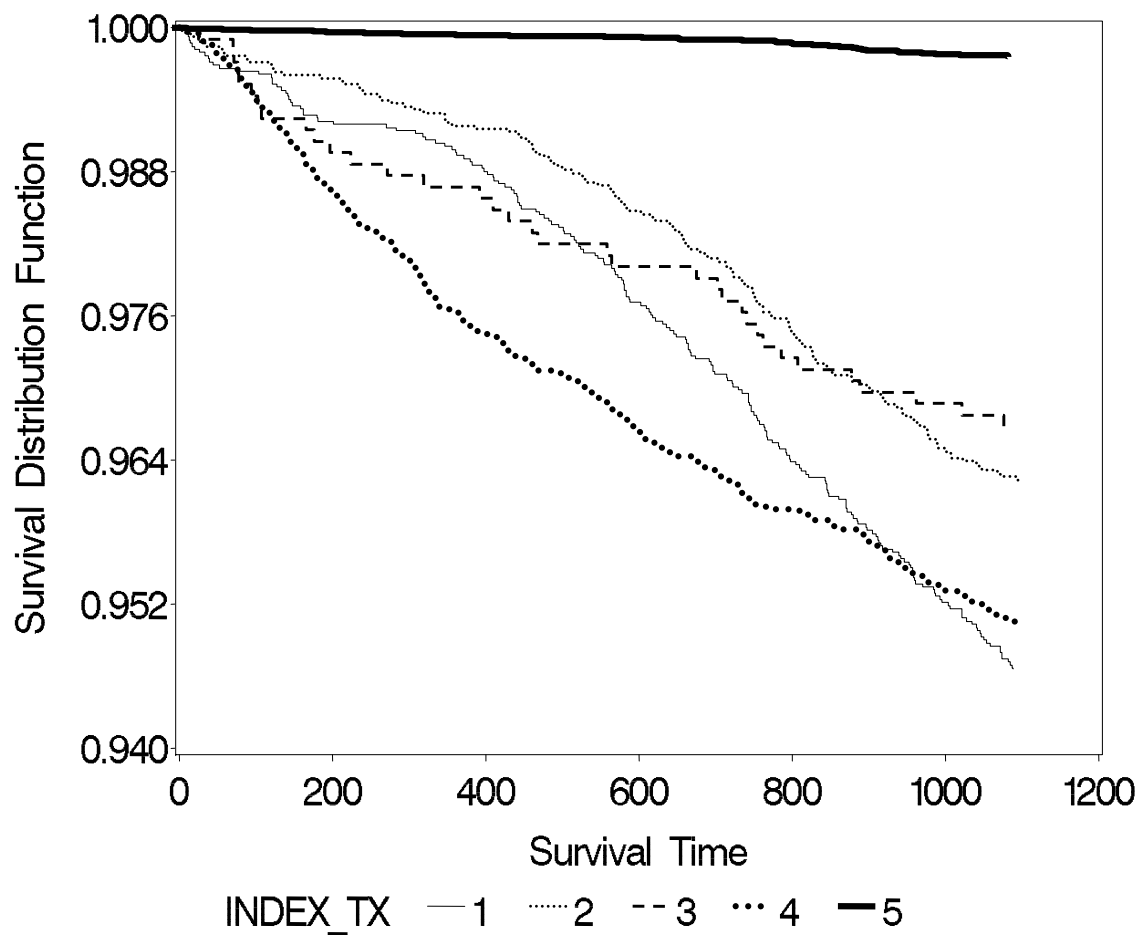
Table 3.42 ITT: Kaplan-Meier Life Table for wrist fracture

Time Interval Intervention Group	Survival	Failure	Survival S.E.	Number Failed	Number Left
6- Month					
ODA	0.9955	0.00452	0.000984	21	4,624
ODAHRT	0.9973	0.00273	0.000788	12	4,379
ODHRT	0.9951	0.00494	0.00174	8	1,612
ODNOTX	0.9958	0.00423	0.000746	32	7,536
NOODTX	1.000	0.000032	0.000032	1	31,626
1 - Year					
ODA	0.9929	0.00710	0.00123	33	4,612
ODAHRT	0.9957	0.00433	0.000991	19	4,372
ODHRT	0.9938	0.00617	0.00195	10	1,610
ODNOTX	0.9911	0.00885	0.00108	67	7,501
NOODTX	0.9999	0.000095	0.000055	3	31,624
1 ½ - Years					
ODA	0.9884	0.0116	0.00157	54	4,591
ODAHRT	0.9927	0.00729	0.00128	32	4,359
ODHRT	0.9907	0.00926	0.00238	15	1,605
ODNOTX	0.9880	0.0120	0.00125	91	7,477
NOODTX	0.9998	0.000158	0.000071	5	31,622
2 - Years					
ODA	0.9826	0.0174	0.00192	81	4,564
ODAHRT	0.9891	0.0109	0.00157	48	4,343
ODHRT	0.9877	0.0123	0.00274	20	1,600
ODNOTX	0.9845	0.0155	0.00142	117	7,451
NOODTX	0.9998	0.000190	0.000077	6	31,621
2 ½ - Years					
ODA	0.9763	0.0237	0.00223	110	4,535
ODAHRT	0.9845	0.0155	0.00186	68	4,323
ODHRT	0.9846	0.0154	0.00306	25	1,595
ODNOTX	0.9818	0.0182	0.00154	138	7,430
NOODTX	0.9998	0.000221	0.000084	7	31,620
3 - Years					
ODA	0.9724	0.0276	0.00240	128	4,517
ODAHRT	0.9813	0.0187	0.00204	82	4,309
ODHRT	0.9821	0.0179	0.00329	29	1,519
ODNOTX	0.9781	0.0219	0.00168	166	7,402
NOODTX	0.9997	0.000285	0.000095	9	31,618

Non Intent-To-Treat Cohort

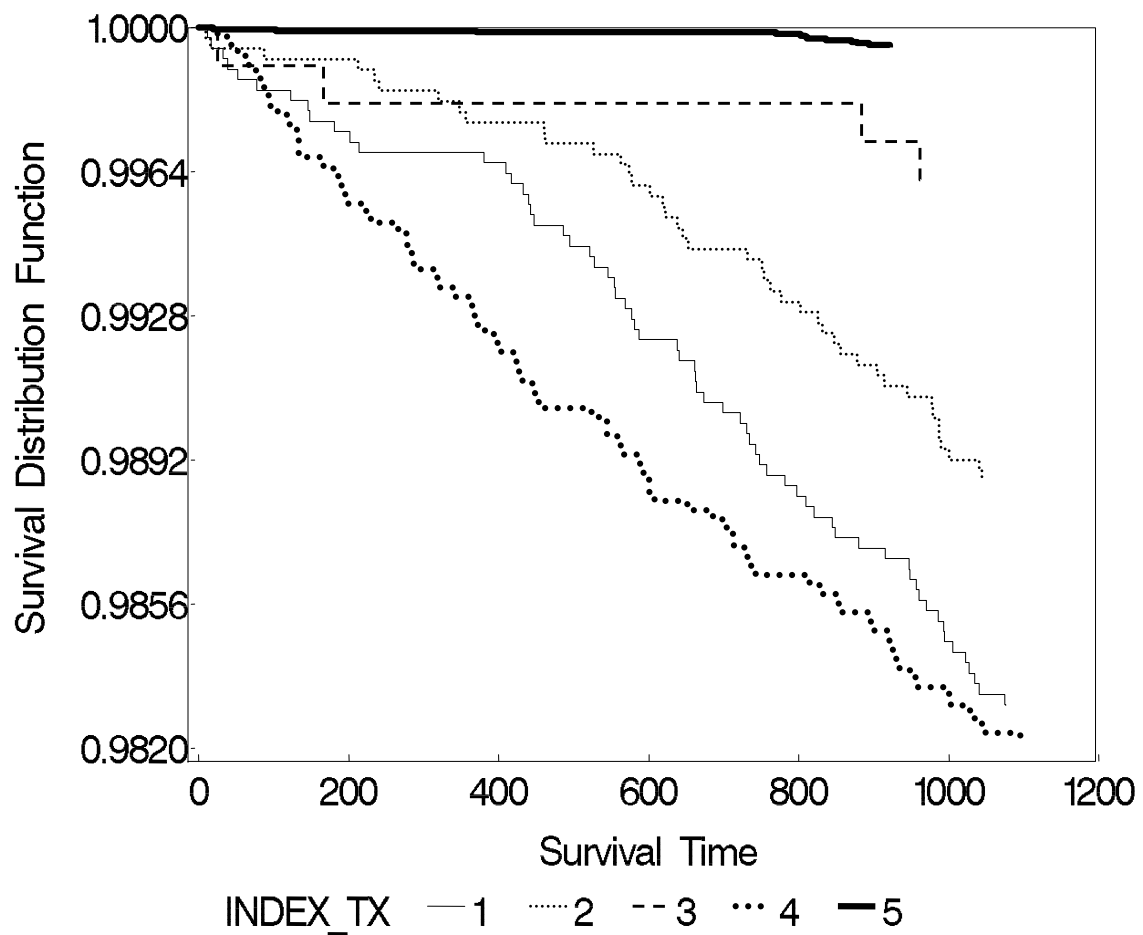
The Kaplan-Meier life tables and survival curves obtained for the non intent-to-treat cohort were similar to those obtained for the intent-to-treat cohort. One notable exception was that the ODHRT intervention group had the greatest probability that a patient would be fracture-free for any fracture after approximately 2 ½ years. Survival plots are presented in Figures 3.6 to 3.9 for: any fracture, hip fracture, vertebral fracture, and wrist fracture, respectively. Tables 3.43 to 3.46 show the Kaplan-Meier life tables for: any fracture, hip fracture, vertebral fracture, and wrist fracture, respectively.

Figure 3.6 Non-ITT: Kaplan-Meier survival curve for any fracture



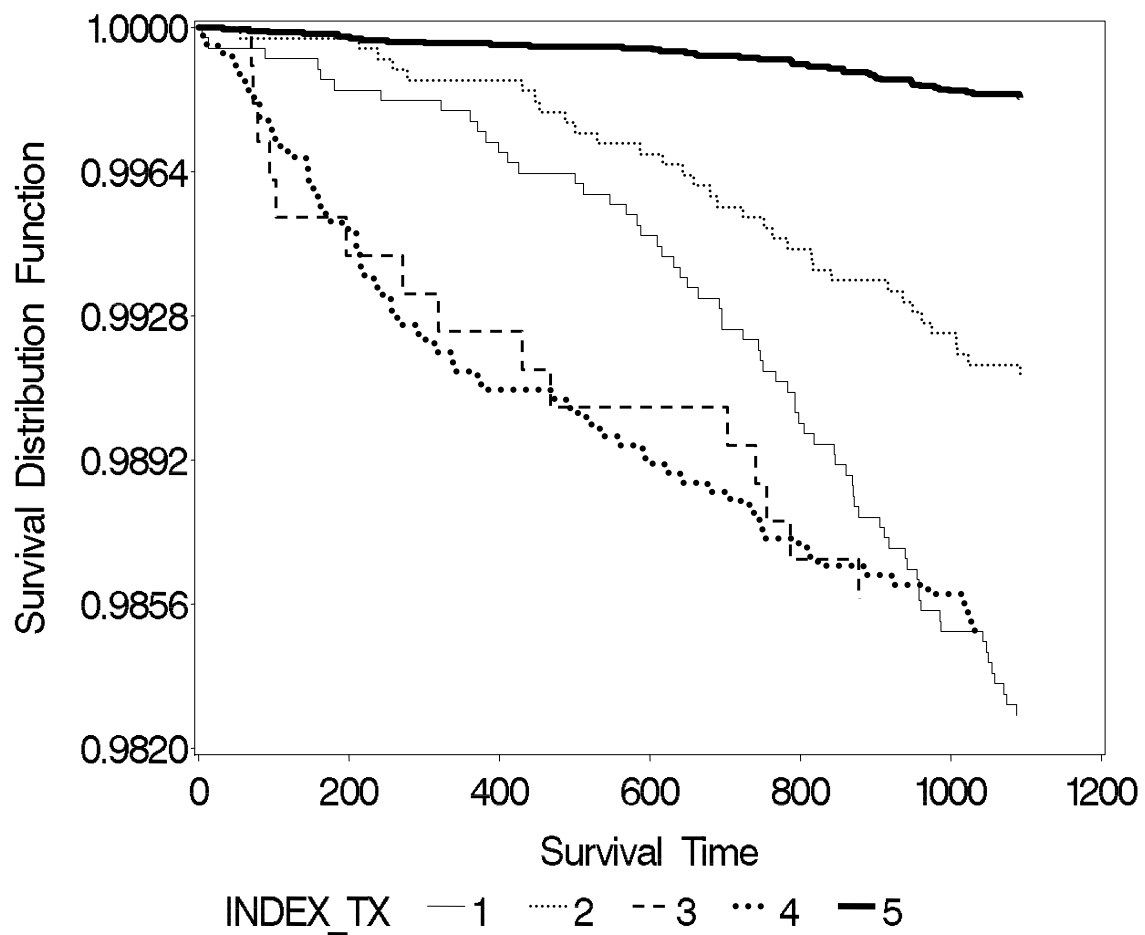
* Index_TX 1: ODA intervention group; Index_TX 2: ODAHRT intervention group;
 Index_TX 3: ODHRT intervention group; Index_TX 4: ODNOTX intervention group;
 Index_TX 5: NOODTX intervention group; Survival Time: Days

Figure 3.7 Non-ITT: Kaplan-Meier survival curve for hip fracture



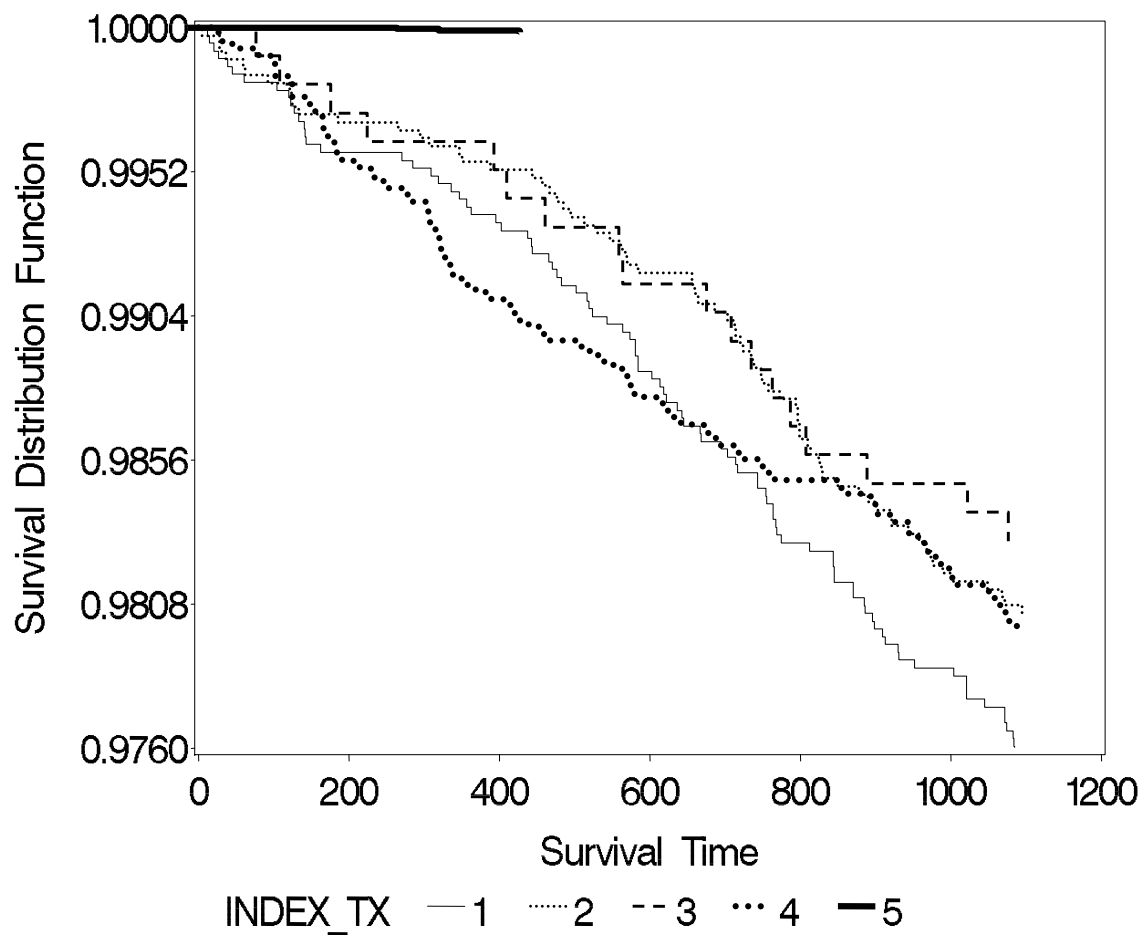
* Index_TX 1: ODA intervention group; Index_TX 2: ODAHRT intervention group;
 Index_TX 3: ODHRT intervention group; Index_TX 4: ODNOTX intervention group;
 Index_TX 5: NOODTX intervention group; Survival Time: Days

Figure 3.8 Non-ITT: Kaplan-Meier survival curve for vertebral fracture



* Index_TX 1: ODA intervention group; Index_TX 2: ODAHRT intervention group;
 Index_TX 3: ODHRT intervention group; Index_TX 4: ODNOTX intervention group;
 Index_TX 5: NOODTX intervention group; Survival Time: Days

Figure 3.9 Non-ITT: Kaplan-Meier survival curve for wrist fracture



* Index_TX 1: ODA intervention group; Index_TX 2: ODAHRT intervention group;
 Index_TX 3: ODHRT intervention group; Index_TX 4: ODNOTX intervention group;
 Index_TX 5: NOODTX intervention group; Survival Time: Days

Table 3.43 Non-ITT: Kaplan-Meier Life Table for any fracture

Time Interval Intervention Group	Survival	Failure	Survival S.E.	Number Failed	Number Left
6- Month					
ODA	0.9925	0.00754	0.00140	29	3,816
ODAHRT	0.9958	0.00421	0.00105	16	3,781
ODHRT	0.9896	0.0104	0.00313	11	1,043
ODNOTX	0.9875	0.0125	0.00169	54	4,259
NOODTX	0.9997	0.000317	0.000112	8	25,266
1 - Year					
ODA	0.9891	0.0109	0.00168	42	3,803
ODAHRT	0.9916	0.00843	0.00148	32	3,765
ODHRT	0.9858	0.0142	0.00365	15	1,039
ODNOTX	0.9757	0.0243	0.00235	105	4,208
NOODTX	0.9994	0.000593	0.000153	15	25,259
1 ½ - Years					
ODA	0.9808	0.0192	0.00222	74	3,771
ODAHRT	0.9868	0.0132	0.00185	50	3,747
ODHRT	0.9810	0.0190	0.00420	20	1,034
ODNOTX	0.9692	0.0308	0.00263	133	4,180
NOODTX	0.9992	0.000752	0.000172	19	25,255
2 - Years					
ODA	0.9698	0.0302	0.00276	116	3,729
ODAHRT	0.9789	0.0211	0.00233	80	3,717
ODHRT	0.9763	0.0237	0.00469	25	1,029
ODNOTX	0.9617	0.0383	0.00292	165	4,148
NOODTX	0.9990	0.00103	0.000202	26	25,248
2 ½ - Years					
ODA	0.9573	0.0427	0.00326	164	3,681
ODAHRT	0.9694	0.0306	0.00279	116	3,681
ODHRT	0.9687	0.0313	0.00536	33	1,021
ODNOTX	0.9566	0.0434	0.00310	187	4,126
NOODTX	0.9981	0.00190	0.000274	48	25,226
3 - Years					
ODA	0.9467	0.0533	0.00362	205	3,640
ODAHRT	0.9621	0.0379	0.00310	144	3,653
ODHRT	0.9668	0.0332	0.00552	35	1,019
ODNOTX	0.9502	0.0498	0.00331	215	4,098
NOODTX	0.9977	0.00233	0.000304	59	25,215

Table 3.44 Non-ITT: Kaplan-Meier Life Tables for hip fracture

Time Interval Intervention Group	Survival	Failure	Survival S.E.	Number Failed	Number Left
6- Month					
ODA	0.9976	0.00237	0.000713	11	4,634
ODAHRT	0.9989	0.00114	0.000509	5	4,386
ODHRT	0.9981	0.00185	0.00107	3	1,617
ODNOTX	0.9968	0.00317	0.000646	24	7,544
NOODTX	0.9999	0.000095	0.000055	3	31,624
1 - Year					
ODA	0.9970	0.00301	0.000804	14	4,631
ODAHRT	0.9975	0.00251	0.000754	11	4,380
ODHRT	0.9975	0.00247	0.00123	4	1,616
ODNOTX	0.9935	0.00647	0.000922	49	7,519
NOODTX	0.9999	0.000095	0.000055	3	31,624
1 ½ - Years					
ODA	0.9944	0.00560	0.00109	26	4,619
ODAHRT	0.9964	0.00364	0.000909	16	4,375
ODHRT	0.9957	0.00432	0.00163	7	1,616
ODNOTX	0.9913	0.00872	0.00107	66	7,502
NOODTX	0.9999	0.000126	0.000063	4	31,623
2 - Years					
ODA	0.9905	0.00947	0.00142	44	4,601
ODAHRT	0.9941	0.00592	0.00116	26	4,365
ODHRT	0.9951	0.00494	0.00174	8	1,612
ODNOTX	0.9885	0.0115	0.00123	87	7,481
NOODTX	0.9998	0.000190	0.000077	6	31,621
2 ½ - Years					
ODA	0.9873	0.0127	0.00164	59	4,586
ODAHRT	0.9911	0.00888	0.00142	39	4,352
ODHRT	0.9932	0.00679	0.00204	11	1,609
ODNOTX	0.9856	0.0144	0.00137	109	7,459
NOODTX	0.9993	0.000664	0.000145	21	31,606
3 - Years					
ODA	0.9836	0.0164	0.00186	76	4,569
ODAHRT	0.9888	0.0112	0.00159	49	4,342
ODHRT	0.9920	0.00802	0.00222	13	1,607
ODNOTX	0.9820	0.0180	0.00153	136	7,432
NOODTX	0.9993	0.000727	0.000152	23	31,604

Table 3.45 Non-ITT: Kaplan-Meier Life Table for vertebral fracture

Time Interval Intervention Group	Survival	Failure	Survival S.E.	Number Failed	Number Left
6- Month					
ODA	0.9983	0.00172	0.000608	8	4,637
ODAHRT	0.9989	0.00114	0.000509	5	4,386
ODHRT	0.9951	0.00494	0.00174	8	1,612
ODNOTX	0.9947	0.00529	0.000833	40	7,528
NOODTX	0.9997	0.000253	0.000089	8	31,619
1 - Year					
ODA	0.9968	0.00323	0.000832	15	4,630
ODAHRT	0.9970	0.00296	0.000820	13	4,378
ODHRT	0.9920	0.00802	0.00222	13	1,607
ODNOTX	0.9902	0.00978	0.00113	74	7,494
NOODTX	0.9996	0.000443	0.000118	14	31,613
1 ½ - Years					
ODA	0.9933	0.00667	0.00119	31	4,614
ODAHRT	0.9948	0.00524	0.00109	23	4,368
ODHRT	0.9883	0.0117	0.00267	19	1,601
ODNOTX	0.9878	0.0122	0.00126	92	7,476
NOODTX	0.9994	0.000632	0.000141	20	31,607
2 – Years					
ODA	0.9886	0.0114	0.00156	53	4,592
ODAHRT	0.9923	0.000774	0.00132	34	4,357
ODHRT	0.9864	0.0136	0.00288	22	1,598
ODNOTX	0.9849	0.0151	0.00140	114	7,454
NOODTX	0.9991	0.000949	0.000173	30	31,597
2 ½ - Years					
ODA	0.9841	0.0159	0.00184	74	4,571
ODAHRT	0.9900	0.0100	0.00150	44	4,347
ODHRT	0.9790	0.0210	0.00356	34	1,586
ODNOTX	0.9811	0.0189	0.00157	143	7,425
NOODTX	0.9980	0.00196	0.000249	62	31,565
3 - Years					
ODA	0.9774	0.0226	0.00218	105	4,540
ODAHRT	0.9870	0.0130	0.00171	57	4,334
ODHRT	0.9790	0.0210	0.00356	34	1,586
ODNOTX	0.9781	0.0219	0.00168	166	7,402
NOODTX	0.9970	0.00288	0.000301	91	31,536

Table 3.46 Non-ITT: Kaplan-Meier Life Table for wrist fracture

Time Interval Intervention Group	Survival	Failure	Survival S.E.	Number Failed	Number Left
6- Month					
ODA	0.9955	0.00452	0.000984	21	4,624
ODAHRT	0.9973	0.00273	0.000788	12	4,379
ODHRT	0.9951	0.00494	0.00174	8	1,612
ODNOTX	0.9958	0.00423	0.000746	32	7,536
NOODTX	1.000	0.000032	0.000032	1	31,626
1 - Year					
ODA	0.9929	0.00710	0.00123	33	4,612
ODAHRT	0.9957	0.00433	0.000991	19	4,372
ODHRT	0.9938	0.00617	0.00195	10	1,610
ODNOTX	0.9911	0.00885	0.00108	67	7,501
NOODTX	0.9999	0.000095	0.000055	3	31,624
1 ½ - Years					
ODA	0.9884	0.0116	0.00157	54	4,591
ODAHRT	0.9927	0.00729	0.00128	32	4,359
ODHRT	0.9907	0.00926	0.00238	15	1,605
ODNOTX	0.9880	0.0120	0.00125	91	7,477
NOODTX	0.9998	0.000158	0.000071	5	31,622
2 - Years					
ODA	0.9826	0.0174	0.00192	81	4,564
ODAHRT	0.9891	0.0109	0.00157	48	4,343
ODHRT	0.9877	0.0123	0.00274	20	1,600
ODNOTX	0.9845	0.0155	0.00142	117	7,451
NOODTX	0.9998	0.000190	0.000077	6	31,621
2 ½ - Years					
ODA	0.9763	0.0237	0.00223	110	4,535
ODAHRT	0.9845	0.0155	0.00186	68	4,323
ODHRT	0.9846	0.0154	0.00306	25	1,595
ODNOTX	0.9818	0.0182	0.00154	138	7,430
NOODTX	0.9998	0.000221	0.000084	7	31,620
3 - Years					
ODA	0.9724	0.0276	0.00240	128	4,517
ODAHRT	0.9813	0.0187	0.00204	82	4,309
ODHRT	0.9821	0.0179	0.00329	29	1,591
ODNOTX	0.9781	0.0219	0.00168	166	7,402
NOODTX	0.9997	0.000285	0.000095	9	31,618

Cox Proportional-Hazards Model

A direct Cox proportional-hazards model was used to assess the relationship between survival time and the set of covariates. The primary purpose of this analysis was to determine if there was a difference in time to fracture between intervention groups after adjusting for the effects of the other covariates. As with the logistic regression analyses, two series of Cox regressions were performed. The first series included all five intervention groups and covariates. The second series included only the active intervention groups and examined age as a continuous variable and oral corticosteroid use with a duration > 1-year.

In both the first series and second series of Cox regression analyses, four separate Cox regressions were performed, one for each type of fracture (any fracture, hip fracture, vertebral fracture, and wrist fracture), to determine the risk of fracture (intervention effectiveness) for each intervention group. For both the first and second series of Cox regressions analyses, the significance of the risk factors and other covariates in the prediction of osteoporotic fracture were determined from the output of the Cox regression analysis for any fracture. While both the treatment categories and the covariates of interest were included in each regression analysis, the results of the treatment effects are described in separate tables from the covariate results.

First Series of Cox Regressions

Intervention Effectiveness (Intent-To-Treat Cohort)

The Cox regression model for the intent-to-treat cohort showed that patients in the ODAHRT and NOODTX intervention groups had a significantly longer survival time

for: any fracture (hazard ratio (HR) = 0.711, 95% hazard ratio confidence limits (CI) 0.590 to 0.856, $p = 0.0003$; HR = 0.68, 95% CI = 0.055 to 0.083, $p < 0.0001$, respectively); for hip fracture (HR = 0.673, 95% CI 0.476 to 0.950, $p = 0.244$; HR = 0.041, 95% CI = 0.026 to 0.064, $p < 0.0001$, respectively); and for vertebral fracture (HR = 0.578, 95% CI 0.420 to 0.796, $p = 0.0008$; HR = 0.141, 95% CI = 0.109 to 0.183, $p < 0.0001$, respectively) compared to those in the ODNOTX intervention group. Only the NOODTX intervention group had statistically significant longer survival time for wrist fracture (HR = 0.013, 95% CI = 0.007 to 0.025, $p < 0.0001$). Table 3.47 shows the Cox proportional hazard regression model for intervention effectiveness parameter estimates.

Table 3.47 FS ITT: Cox regression model for intervention effectiveness parameter estimates

Fracture Type Intervention Group	Estimate	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Any					
ODA	-0.09021	0.2815	0.914	0.775	1.077
ODAHRT	-0.34159	0.0003	0.711	0.590	0.856
ODHRT	-0.14307	0.2913	0.867	0.664	1.130
NOODTX	-2.69278	< 0.0001	0.068	0.055	0.083
Hip					
ODA	-0.23707	0.1216	0.789	0.584	1.065
ODAHRT	-0.39659	0.0244	0.673	0.476	0.950
ODHRT	-0.48994	0.1059	0.613	0.338	1.109
NOODTX	-3.20020	< 0.0001	0.041	0.026	0.064
Vertebral					
ODA	-0.14777	0.2767	0.863	0.661	1.126
ODAHRT	-0.54746	0.0008	0.578	0.420	0.796
ODHRT	0.08402	0.6739	1.088	0.735	1.609
NOODTX	-1.95883	< 0.0001	0.141	0.109	0.183
Wrist					
ODA	0.09725	0.4588	1.102	0.852	1.426
ODAHRT	-0.19322	0.1862	0.824	0.619	1.098
ODHRT	-0.15262	0.4786	0.858	0.563	1.309
NOODTX	-4.34873	< 0.0001	0.013	0.007	0.025

* Bolded = $p < 0.05$

Risk Factor Significance (Intent-To-Treat Cohort)

Risk factors age, previous osteoporotic fracture, and corticosteroid use were shown to significantly decrease survival time, whereas intervention compliance and statin use were shown to significantly increase survival time. Using age-category 50-54 as the reference category, the survival time decreased significantly with each successive increase in age-category (age-category 55 to 59: HR = 1.406, 95% CI = 1.082 to 1.825, $p = 0.0106$; age-category 60 to 64: HR = 1.581, 95% CI = 1.242 to 2.012, $p = 0.0002$; age-category 65 to 69: HR = 1.846, 95% CI = 1.403 to 2.429, $p < 0.0001$; age-category 70 to 74: HR = 2.628, 95% CI = 1.994 to 3.465, $p < 0.0001$; age-category 75 to 79: HR =

2.961, 95% CI = 2.256 to 3.885, $p < 0.0001$; age-category 80 to 84: HR = 4.418, 95% CI = 3.274 to 5.961, $p < 0.0001$; age-category ≥ 85 : HR = 5.555, 95% CI = 3.962 to 7.787, $p < 0.0001$). Likewise, a previous osteoporotic fracture was shown to significantly decrease survival time (HR = 3.863, 95% CI = 3.150 to 4.737, $p < 0.0001$).

Evidence supporting a decreased survival time relative to corticosteroid dose and duration use was not as conclusive. Only corticosteroid dose/duration categories $<5\text{mg}/>365$ days and $>10\leq 20\text{mg}/>365$ days were found to significantly decrease survival time (corticosteroid dose/duration category $<5\text{mg}/>365$ days: HR = 1.640, 95% CI = 1.124 to 2.393, $p = 0.0103$; corticosteroid dose/duration category: $>10\leq 20\text{mg}/>365$ days: HR = 2.054, 95% CI = 1.343 to 3.142, $p = 0.0009$).

Intervention compliance was shown to have an additional protective effect when compared to non-compliance for the ODAHRT intervention group (HR = 0.622, 95% CI = 0.401 to 0.964, $p = 0.0338$). Statin use was shown to have a statistically significant protective effective for osteoporotic fracture for low dose statin for each level of duration (statin dose/duration category: low/ ≤ 1 year: HR = 0.416, 95% CI = 0.313 to 0.552, $p < 0.0001$; statin dose/duration category: low/ $>1\leq 2$ years: HR = 0.631, 95% CI = 0.478 to 0.834, $p < 0.0012$; statin dose/duration category: low/ >2 years: HR = 0.659, 95% CI = 0.535 to 0.813, $p = 0.0001$) and for high dose statin dose/duration category - high/ ≤ 1 year (HR = 0.424, CI = 0.245 to 0.734, $p = 0.0022$). Table 3.48 shows the Cox proportional hazard regression model for risk factor parameter estimates.

Table 3.48 FS ITT: Cox regression model for risk factor parameter estimates

Parameter	Estimate	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Age Category					
55 - 59	0.34047	0.0016	1.406	1.082	1.825
60 – 64	0.45790	0.0002	1.581	1.242	2.012
64 – 69	0.61312	< 0.0001	1.846	1.403	2.429
70 – 74	0.96629	< 0.0001	2.628	1.994	3.465
75 – 79	1.08540	< 0.0001	2.961	2.256	3.885
80 – 84	1.48560	< 0.0001	4.418	3.274	5.961
≥ 85	1.71462	< 0.0001	5.555	3.962	7.787
Compliance					
ODA 80% MPR	-0.29676	0.0579	0.743	0.547	1.010
ODHRT 80% MPR	-0.24019	0.5226	0.786	0.377	1.642
ODAHRT 80% MPR	-0.47452	0.0338	0.622	0.401	0.964
Corticosteroid Use					
<5mg; ≤180 days	-0.66644	0.1041	0.514	0.230	1.147
<5mg; >180≤365 days	-10.2942	0.9481	0.000	0.000	0.000
<5mg; >365 days	0.49477	0.0103	1.640	1.124	2.393
≥5≤10mg; ≤180 days	-0.02246	0.8925	0.978	0.706	1.354
≥5≤10mg; >180≤ 365 days	-0.72854	0.2082	0.483	0.155	1.501
≥5≤10mg; >365 days	0.30868	0.0676	1.362	0.978	1.896
>10≤ 20mg; ≤180 days	-0.10760	0.5020	0.898	0.656	1.229
>10≤ 20mg; >180≤365 days	0.30769	0.3871	1.360	0.677	2.732
>10≤ 20mg; >365 days	0.71975	0.0009	2.054	1.343	3.142
>20mg; ≤180 days	-0.03958	0.7404	0.961	0.761	1.215
>20mg; >180≤365 days	0.77532	0.0589	2.171	0.971	4.854
>20mg; >365 days	0.47317	0.5044	1.605	0.400	6.439
Statin Use					
Low; ≤1 year	-0.87712	< 0.0001	0.416	0.313	0.552
Low; >1≤ 2 years	-0.46032	0.0012	0.631	0.478	0.834
Low; >2 years	-0.41657	< 0.0001	0.659	0.535	0.813
High; ≤1 year	-0.85716	0.0022	0.424	0.245	0.734
High; >1≤ 2 years	-0.44218	0.0717	0.643	0.397	1.040
High; >2 years	-0.28294	0.1028	0.754	0.536	1.059
Previous Fracture					
Previous Fracture	1.35140	< 0.0001	3.863	3.150	4.737

* Bolded = p < 0.05

Intervention Effectiveness (Non Intent-To-Treat Cohort)

Comparison of the intervention effectiveness results of obtained for the non intent-to-treat cohort to the intent-to-treat cohort revealed two significant differences. First, the ODAHRT intervention group was found to only have a statistically significant longer survival time for vertebral fracture. Second, the ODHRT intervention group was found to have a statistically significant longer survival time for hip fracture. Table 3.49 provides the Cox proportional hazard regression model for intervention effectiveness parameter estimates.

Table 3.49 FS Non-ITT: Cox regression model for intervention effectiveness parameter estimates

Fracture Type Intervention Group	Estimate	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Any					
ODA	-0.01264	0.9047	0.987	0.803	1.215
ODAHRT	-0.21111	0.0663	0.810	0.646	1.014
ODHRT	-0.18109	0.3503	0.834	0.571	1.220
NOODTX	-3.03966	< 0.0001	0.048	0.036	0.064
Hip					
ODA	-0.13077	0.4650	0.877	0.618	1.246
ODAHRT	-0.28813	0.1548	0.750	0.504	1.115
ODHRT	-1.28014	0.0304	0.278	0.087	0.886
NOODTX	-3.57540	< 0.0001	0.028	0.015	0.052
Vertebral					
ODA	0.04783	0.7986	1.049	0.726	1.515
ODAHRT	-0.50976	0.0259	0.601	0.384	0.940
ODHRT	0.23467	0.4308	1.264	0.705	2.267
NOODTX	-2.06741	< 0.0001	0.127	0.086	0.187
Wrist					
ODA	0.07846	0.6337	1.082	0.783	1.494
ODAHRT	-0.03974	0.8158	0.961	0.688	1.343
ODHRT	-0.08358	0.7668	0.920	0.529	1.598
NOODTX	-5.13391	< 0.0001	0.006	0.002	0.019

* Bolded = p < 0.05

Risk Factor Significance (Non Intent-To-Treat Cohort)

Comparison of risk factor significance results of obtained for the non intent-to-treat cohort to the intent-to-treat cohort also revealed two major differences. First, the ODAHRT intervention compliance no longer afforded an additional statistically significant protective effect. Second, the corticosteroid dose/duration category $\geq 5 \leq 10 \text{mg} / > 365$ days no longer had a statistically significant decreased survival time. Table 3.50 provides the Cox proportional hazard regression model for risk factor parameter estimates.

Table 3.50 FS Non-ITT: Cox regression model for risk factor parameter estimates

Parameter	Estimate	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Age Category					
55 - 59	0.24534	0.1535	1.278	0.913	1.790
60 – 64	0.36342	0.0219	1.438	1.054	1.962
64 – 69	0.48761	0.0060	1.628	1.150	2.305
70 – 74	0.83275	< 0.0001	2.300	1.622	3.261
75 – 79	1.01626	< 0.0001	2.763	1.968	3.880
80 – 84	1.27665	< 0.0001	3.585	2.433	5.282
≥ 85	1.64897	< 0.0001	5.202	3.426	7.898
Compliance					
ODA 80% MPR	-0.30187	0.0945	0.739	0.519	1.053
ODHRT 80% MPR	-0.38346	0.4708	0.682	0.240	1.932
ODAHRT 80% MPR	-0.40512	0.0866	0.667	0.420	1.060
Corticosteroid Use					
<5mg; ≤180 days	-82806	0.1530	0.437	0.140	1.360
<5mg; >180≤365 days	-10.2410	0.9588	0.000	0.000	0.000
<5mg; >365 days	0.51262	0.0386	1.670	1.027	2.714
≥5≤10mg; ≤180 days	0.17960	0.3480	1.197	0.822	1.714
≥5≤10mg; >180≤ 365 days	-1.28922	0.1980	0.275	0.039	1.961
≥5≤10mg; >365 days	0.09671	0.6881	1.102	0.687	1.766
>10≤ 20mg; ≤180 days	-0.08497	0.6791	0.919	0.614	1.374
>10≤ 20mg; >180≤365 days	0.08473	0.8661	1.088	0.406	2.915
>10≤ 20mg; >365 days	0.69705	0.0134	2.008	1.155	3.490
>20mg; ≤180 days	-0.07835	0.6120	0.925	0.683	1.252
>20mg; >180≤365 days	0.23751	0.7377	1.268	0.316	5.091
>20mg; >365 days	0.17110	0.8644	1.187	0.167	8.456
Statin Use					
Low; ≤1 year	-0.90012	< 0.0001	0.407	0.279	0.592
Low; >1≤ 2 years	-0.49964	0.0081	0.607	0.419	0.878
Low; >2 years	-0.40327	0.0027	0.668	0.513	0.869
High; ≤1 year	-0.79869	0.0252	0.450	0.224	0.905
High; >1≤ 2 years	-0.42491	0.2072	0.654	0.338	1.265
High; >2 years	-0.26639	0.2239	0.766	0.499	1.177
Previous Fracture					
Previous Fracture	1.18617	< 0.0001	3.275	2.486	4.312

* Bolded = p < 0.05

Second Series of Cox Regressions

As with the second series of logistic regression analyses, the second series of Cox regressions involved only those intervention groups with a diagnosis of osteoporosis. Similar to the logistic regression analyses, the first series of Cox regression analyses revealed that the risk of an osteoporotic fracture event increased with each successive increase in age-category. Likewise, the first series of Cox regression analyses suggested that possibly only long-term use of oral corticosteroids was associated with a statistically significant increased risk of osteoporotic fracture. Therefore, in the second series of Cox regression analyses, age was treated as a continuous variable and only long-term (length of oral corticosteroid use > 1-year) oral corticosteroid use was assessed as a risk factor.

A comparison of the Cox regression intervention effectiveness parameter estimates of the second series of Cox regression analyses to the first series for the intent-to-treat cohort revealed no differences as to which intervention groups had a statistically significant decreased risk of osteoporotic fracture among the active intervention groups. A comparison of the Cox regression intervention effectiveness parameter estimates of the second series of Cox regression analyses to the first series for the non intent-to-treat cohort revealed one major difference. In the second series, the ODHRT group was found to have a statistically significant decreased risk of any osteoporotic fracture.

Results from the second series of Cox regression risk factor parameter estimates for both the intent-to-treat and non intent-to-treat cohorts revealed that for each one-year increase in age there was a statistically significant increased risk of osteoporotic fracture (RH = 1.044, 95% CI = 1.037 to 1.051, $p < 0.0001$; RH = 1.045, 95% CI = 1.036 to 1.053, $p < 0.0001$, respectively). Results for both cohorts also showed that oral corticosteroid use for a duration of > 1-year was associated with a statistically significant increased risk of osteoporotic fracture (RH = 1.518, 95% CI = 1.210 to 1.905, $p = 0.0003$;

RH = 1.370, 95% CI = 1.010 to 1.859, $p = 0.0429$). As for the other risk factors and covariates, the results obtained for the second series of Cox regression risk factor parameter estimates paralleled those obtained for their respective cohorts in the first series of Cox regression analyses. Tables 3.51 to 3.54 show the results for the second series of Cox regressions.

Table 3.51 SS ITT: Cox regression model intervention effectiveness parameter estimates

Parameter	Estimate	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Any					
ODA	-0.07764	0.3480	0.925	0.787	1.088
ODAHRT	-0.34515	0.0002	0.708	0.589	0.851
ODHRT	-0.15433	0.2550	0.857	0.657	1.118
Hip					
ODA	-0.24234	0.1074	0.785	0.584	1.054
ODAHRT	-0.41928	0.0161	0.658	0.467	0.925
ODHRT	-0.48873	0.1067	0.613	0.339	1.111
Vertebral					
ODA	-0.12631	0.3470	0.881	0.677	1.147
ODAHRT	-0.53868	0.0009	0.584	0.425	0.801
ODHRT	0.07433	0.7100	1.077	0.728	1.594
Wrist					
ODA	0.14091	0.2762	1.151	0.893	1.484
ODAHRT	-0.16861	0.2436	0.845	0.636	1.122
ODHRT	-0.16591	0.4410	0.847	0.555	1.292

* Bolded = $p < 0.05$

Table 3.52 SS ITT: Cox regression model risk factor parameter estimates

Parameter	Estimate	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Age Category					
Age	0.04310	< 0.0001	1.044	1.037	1.051
Compliance					
ODA 80% MPR	-0.29163	0.0620	0.747	0.550	1.015
ODHRT 80% MPR	-0.22859	0.5427	0.796	0.381	1.661
ODAHRT 80% MPR	-0.48399	0.0303	0.616	0.398	0.955
Corticosteroid Use					
≤ 1-year	-0.10024	0.2540	0.905	0.761	1.075
> 1-year	0.41753	0.0003	1.518	1.210	1.905
Statin Use					
Low; ≤1 year	-0.87735	< 0.0001	0.416	0.308	0.562
Low; >1≤ 2 years	-0.47557	0.0016	0.622	0.463	0.835
Low; >2 years	-0.42119	0.0001	0.656	0.528	0.815
High; ≤1 year	-0.73683	0.0085	0.479	0.276	0.829
High; >1≤ 2 years	-0.45919	0.0786	0.632	0.379	1.054
High; >2 years	-0.36333	0.0517	0.695	0.482	1.003
Previous Fracture					
Previous Fracture	1.36320	< 0.0001	3.909	3.190	4.790

* Bolded = p < 0.05

Table 3.53 SS Non-ITT: Cox regression model intervention effectiveness parameter estimates

Fracture Type Intervention Group	Estimate	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Any					
ODA	-0.01535	0.8829	0.985	0.803	1.208
ODAHRT	-0.22386	0.0490	0.799	0.640	0.999
ODHRT	-0.18162	0.3487	0.834	0.570	1.219
Hip					
ODA	-0.12730	0.4691	0.880	0.624	1.243
ODAHRT	-0.29280	0.1441	0.746	0.504	1.105
ODHRT	-1.24407	0.0353	0.288	0.090	0.918
Vertebral					
ODA	0.04868	0.7927	1.050	0.730	1.509
ODAHRT	-0.52196	0.0216	0.593	0.380	0.926
ODHRT	0.22988	0.4412	1.258	0.701	2.259
Wrist					
ODA	0.10572	0.5156	1.112	0.808	1.529
ODAHRT	-0.02056	0.9029	0.980	0.704	1.363
ODHRT	-0.10048	0.7211	0.904	0.521	1.570

* Bolded = $p < 0.05$

Table 3.54 SS Non-ITT: Cox regression model risk factor parameter estimates

Parameter	Estimate	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Age Category					
Age	0.04357	< 0.0001	1.045	1.036	1.053
Compliance					
ODA 80% MPR	-0.30083	0.0951	0.740	0.520	1.054
ODHRT 80% MPR	-0.35696	0.5019	0.700	0.247	1.984
ODAHRT 80% MPR	-0.40919	0.0833	0.664	0.418	1.055
Corticosteroid Use					
≤ 1-year	-0.11126	0.3177	0.895	0.719	1.113
> 1-year	0.31517	0.0429	1.370	1.010	1.859
Statin Use					
Low; ≤1 year	-0.91317	< 0.0001	0.401	0.270	0.596
Low; >1≤ 2 years	-0.45782	0.0170	0.633	0.434	0.921
Low; >2 years	-0.42493	0.0021	0.654	0.499	0.857
High; ≤1 year	-0.70478	0.0483	0.494	0.246	0.995
High; >1≤ 2 years	-0.58364	0.1257	0.558	0.264	1.177
High; >2 years	-0.26766	0.2319	0.765	0.493	1.187
Previous Fracture					
Previous Fracture	1.19696	< 0.0001	3.310	2.516	4.356

* Bolded = p < 0.05

OBJECTIVES 5 AND 6

The logistic regression and direct Cox proportional-hazards regression models employed in objectives 2 and 4, respectively, provided the ability to determine the effectiveness of the osteoporosis treatment interventions while statistically controlling for the presence of risk factors and other covariates. In objective 5, the cost-effectiveness of the treatment interventions is determined while statistically controlling for the presence of risk factors and other covariates in the heterogeneous observational data set by employing the net-benefit regression method of cost-effectiveness analysis. This same methodology is employed in objective 6, where the importance of covariates on the marginal cost-effectiveness of an intervention is determined by examining interaction effects between each intervention and important patient subgroups.

In this analysis, the direct treatment costs (cost of osteoporosis medications and fracture treatment costs) for the three-year observation period were examined from the perspective of the DoD. The change in quality-adjusted life-years over the observation period was the main effectiveness measure and was calculated as described in the methodology section. The net monetary benefits were calculated by employing λ values of \$0, \$30,000, \$60,000, and \$100,000. The work performed in objectives 2 through 4 identified the following set of clinically significant covariates to be included in the model: age ≥ 65 , oral corticosteroid use duration > 1 -year, statin use, and prior osteoporotic fracture. The covariate intervention compliance was dropped from these analyses because it afforded no statistically significant protective effect for intervention groups ODA and ODHRT and ODAHRT compliant patients did not achieve much better outcomes when compared to the ODAHRT intervention group.

As in the previous analyses, two separate analyses were performed, one for the intent-to-treat cohort and the other for the non intent-to-treat cohort. For each cohort, two

separate analyses were initially performed, one without treatment interaction and the other with treatment interaction. Results from these primary analyses provided evidence of a statistically significant positive incremental net-benefit for interaction terms formed between the active intervention groups and covariates age ≥ 65 and prior fracture. Therefore, subsequent post-hoc analyses were performed to determine if any of the active interventions were cost-effective in these sub-groups.

Presented first, for each of the cohorts, are the results of the net-benefit regression analysis without treatment interaction. This analysis provides an estimate of the overall cost-effectiveness of the interventions. The second analysis presented includes treatment interaction, which provides an estimate of how the covariates impact the estimate of the intervention's incremental net-benefit. Lastly, the post-hoc analyses examining the cost-effectiveness of the active intervention groups in the specific sub-groups (patients with a prior fracture or age ≥ 65) are presented.

Before the net-benefit regression results for the primary analyses are presented, the estimated mean total cost and mean change in QALYs is provided for each of the intervention groups for both the intent-to-treat and non intent-to-treat cohorts in Table 3.55. The purpose of this table is to provide background information, which may facilitate an understanding of the net-benefit regression results.

Table 3.55 Primary Analyses: Mean total cost and mean total QALYs by intervention group for the intent-to-treat and non intent-to-treat cohorts

Intervention Group	N	Variable	Mean	Standard Deviation	Minimum	Maximum
Intent-to-Treat Cohort						
ODA	4,645	Total Cost	996.84	1,723.07	9.03	67,635.80
		Total QALYS	-0.0062	0.0344	-0.5372	0
ODAHRT	4,391	Total Cost	1,415.22	1,390.87	45.15	34,898.42
		Total QALYS	-0.0042	0.2790	-0.3791	0
ODHRT	1,620	Total Cost	347.77	1,535.65	0	39,828.32
		Total QALYS	-0.0049	0.0323	-0.5307	0
ODNOTX	7,568	Total Cost	183.68	2,012.09	0	82,598.00
		Total QALYS	-0.0076	0.0417	-0.7573	0
Non Intent-to-Treat Cohort						
ODA	3,845	Total Cost	1,023.87	1,824.44	9.03	67,635.80
		Total QALYS	-0.0058	0.0334	-0.5307	0
ODAHRT	3,797	Total Cost	1,448.71	1,343.43	45.15	25,734.06
		Total QALYS	-0.0038	0.0266	-0.3791	0
ODHRT	1,054	Total Cost	319.96	1,473.09	0	39,828.32
		Total QALYS	-0.0032	0.0261	-0.5307	0
ODNOTX	4,313	Total Cost	197.01	2,280.25	0	82,598.00
		Total QALYS	-0.0071	0.0412	-0.7572	0

Primary Analyses

Intent-To-Treat Cohort

In the analysis without treatment interaction, the coefficients of primary importance are those on the treatment dummy, which correspond to the incremental net-benefit. The coefficients for the covariates describe the impact on average net-benefits and are not of direct interest. In general, examination of the treatment dummy coefficients in comparison to the constant term (control group) coefficient reveals that the incremental net-benefit for all active treatment interventions were less than the incremental net-benefit for the control group (no treatment). More specifically, the incremental net-benefit for treatment with alendronate and the combination of alendronate and HRT were statistically significantly less than no treatment for all values

of λ . In contrast, examination of the coefficients for treatment with HRT reveals that the incremental net-benefit, although lower, was not statistically significantly lower than no treatment at λ values $\geq \$30,000$. The net-benefit regression results for the intent-to-treat cohort are presented in Table 3.56.

Table 3.56 ITT: Net-benefit regression estimates without treatment interaction

N = 18,224 Explanatory Variables	NMB with $\lambda = \$0$ [se] (p-value)	NMB with $\lambda = \$30,000$ [se] (p-value)	NMB with $\lambda = \$60,000$ [se] (p-value)	NMB with $\lambda = \$100,000$ [se] (p-value)
Constant term	-126 [24] (< 0.0001)	-334 [32] (< 0.0001)	-542 [44] (< 0.0001)	-820 [61] (< 0.0001)
<i>Covariates</i>				
Age ≥ 65	-254 [28] (< 0.0001)	-404 [39] (< 0.0001)	-554 [53] (< 0.0001)	-753 [74] (< 0.0001)
Steroid > 1 -year	-136 [57] (0.0161)	-308 [39] (< 0.0001)	-480 [105] (< 0.0001)	-709 [146] (< 0.0001)
Statin	65 [27] (0.0175)	184 [37] (< 0.0001)	303 [51] (< 0.0001)	462 [71] (< 0.0001)
Prior fracture	-420 [77] (< 0.0001)	-1,108 [105] (< 0.0001)	-1,795 [143] (< 0.0001)	-2,712 [200] (< 0.0001)
<i>Treatment dummy</i>				
ODA	-736 [34] (< 0.0001)	-649 [46] (< 0.0001)	-562 [63] (< 0.0001)	-447 [88] (< 0.0001)
ODAHRT	-1,185 [34] (< 0.0001)	-1,049 [45] (< 0.0001)	-913 [62] (< 0.0001)	-732 [87] (< 0.0001)
ODHRT	-189 [48] (< 0.0001)	-117 [66] (0.0744)	-46 [90] (0.6086)	49 [125] (0.6946)
R-squared (adjusted)	0.0849	0.0519	0.0353	0.0267
F(7,1826)	242.43	143.54	96.32	72.31
Prob $> F$	< 0.0001	< 0.0001	< 0.0001	< 0.0001

In the second analysis with treatment interaction, interaction terms were formed between each of the active intervention groups and covariates: age ≥ 65 , steroid > 1 -year, and prior fracture. In this analysis, the coefficients of primary importance are those for the interaction terms. In general, all of the treatment interactions achieved a positive incremental net-benefit. In other words, it was more cost-effective to treat patients in the

covariate sub-group compared to patients not in the covariate subgroup. More specifically, the net-benefit regression results show that for the ODA intervention group there was a statistically significant interaction with age; patients age ≥ 65 achieved higher net-benefits from treatment in comparison to patients < 65 for values of $\lambda \leq \$30,000$. There was also a statistically significant interaction between the ODA intervention group and prior fracture; patients with a prior fracture achieved higher net-benefits from treatment in comparison to patients without a prior fracture for values of $\lambda \geq \$30,000$. Similarly, the ODAHRT intervention group was found to have statistically significant interactions with age and prior fracture. The regression results show that for the ODAHRT intervention group, patients \geq age 65 achieved higher net-benefits from treatment in comparison to patients < 65 for all values of λ . Likewise, patients in the ODAHRT intervention group with a prior fracture achieve higher net-benefits from treatment in comparison to patients without a prior fracture for all values of λ . The only significant interaction term formed between the ODHRT intervention group and a covariate was with prior fracture and this interaction term only became statistically significant at $\lambda \geq \$60,000$. Although higher net-benefits were observed for the interaction terms formed between intervention groups and the covariate corticosteroid use duration > 1 -year, none of these were found to be statistically significant. The net-benefit regression with treatment interaction results for the intent-to-treat cohort are presented in Table 3.57.

Table 3.57 ITT: Net-benefit regression estimates with treatment interaction

N = 18,224	NMB with	NMB with	NMB with	NMB with
Explanatory	$\lambda = \$0$ [se]	$\lambda = \$30,000$ [se]	$\lambda = \$60,000$ [se]	$\lambda = \$100,000$ [se]
Variables	(p-value)	(p-value)	(p-value)	(p-value)
Constant term	-72 [26] (= 0.0048)	-265 [35] (< 0.0001)	-457 [48] (< 0.0001)	-714 [67] (< 0.0001)
<i>Covariates</i>				
Age ≥ 65	-416 [47] (< 0.0001)	-600 [64] (< 0.0001)	-784 [87] (< 0.0001)	-1029 [121] (< 0.0001)
Steroid > 1-year	-253 [96] (0.0084)	-438 [131] (0.0008)	-622 [179] (0.0005)	-868 [250] (0.0005)
Statin	63 [27] (0.0175)	181 [37] (< 0.0001)	300 [51] (< 0.0001)	458 [71] (< 0.0001)
Prior fracture	-420 [77] (0.0204)	-1633 [174] (< 0.0001)	-2582 [238] (< 0.0001)	-3848 [332] (< 0.0001)
<i>Treatment dummy</i>				
ODA	-809 [46] (< 0.0001)	-729 [63] (< 0.0001)	-649 [85] (< 0.0001)	-542 [119] (< 0.0001)
ODAHRT	-1328 [42] (< 0.0001)	-1241 [58] (< 0.0001)	-1153 [80] (< 0.0001)	-1037 [111] (< 0.0001)
ODHRT	-259 [53] (< 0.0001)	-220 [73] (0.0028)	-180 [100] (0.0724)	-127 [139] (0.3641)
<i>Treatment-covariate interactions</i>				
ODA	206 [70]	215 [95]	224 [130]	236 [181]
Age ≥ 65	(0.0031)	(0.0233)	(0.0834)	(0.1920)
ODAHRT	328 [71]	432 [97]	536 [133]	675 [185]
Age ≥ 65	(< 0.001)	(< 0.0001)	(< 0.0001)	(0.0003)
ODHRT	218 [135]	301 [184]	385 [251]	496 [351]
Age ≥ 65	(0.1079)	(0.1022)	(0.1260)	(0.1579)
ODA	99 [146]	131 [199]	162 [271]	204 [379]
Steroid > 1-year	(0.4971)	(0.5112)	(0.5502)	(0.5904)
ODAHRT	218 [138]	208 [188]	199 [256]	186 [358]
Steroid > 1-year	(0.1139)	(0.2672)	(0.4382)	(0.6041)
ODHRT	340 [243]	458 [330]	577 [451]	735 [630]
Steroid > 1-year	(0.1616)	(0.1654)	(0.2006)	(0.2433)
ODA	176 [192]	540 [261]	904 [356]	1390 [498]
Prior fracture	(0.3599)	(0.0387)	(0.0111)	(0.0052)
ODAHRT	773 [202]	1244 [275]	1716 [376]	2344 [525]
Prior fracture	(0.0001)	(< 0.0001)	(< 0.0001)	(< 0.0001)
ODHRT	301 [26]	695 [367]	1089 [500]	1614 [669]
Prior fracture	(0.2636)	(0.581)	(0.0296)	(0.0210)
R-squared (adjusted)	0.0865	0.0537	0.0379	0.0290
F(16,18,207)	108.87	65.69	44.80	34.04
Prob > F	< 0.0001	< 0.0001	< 0.0001	< 0.0001

Non Intent-To-Treat Cohort

The results obtained for the non intent-to-treat cohort mirrored those obtained for the intent-to-treat cohort for the net-benefit regression without treatment interaction. Table 3.58 shows the results of the net-benefit regression without treatment interaction for the non intent-to-treat cohort.

Table 3.58 Non-ITT: Net-benefit regression estimates without treatment interaction

N = 13,008 Explanatory Variables	NMB with $\lambda = \$0$ [se] (p-value)	NMB with $\lambda = \$30,000$ [se] (p-value)	NMB with $\lambda = \$60,000$ [se] (p-value)	NMB with $\lambda = \$100,000$ [se] (p-value)
Constant term	-129 [32] (< 0.0001)	-315 [42] (< 0.0001)	-500 [56] (< 0.0001)	-748 [77] (< 0.0001)
<i>Covariates</i>				
Age ≥ 65	-233 [34] (< 0.0001)	-369 [45] (< 0.0001)	-506 [60] (< 0.0001)	-687 [83] (< 0.0001)
Steroid > 1 -year	-127 [71] (0.0763)	-275 [94] (0.0033)	-424 [125] (0.0007)	-623 [172] (0.0003)
Statin	49 [34] (0.1492)	140 [44] (0.0016)	232 [59] (< 0.0001)	354 [81] (< 0.0001)
Previous fracture	-464 [96] (< 0.0001)	-981 [126] (< 0.0001)	-1498 [168] (< 0.0001)	-2187 [231] (< 0.0001)
<i>Treatment dummy</i>				
ODA	-762 [42] (< 0.0001)	-685 [55] (< 0.0001)	-608 [73] (< 0.0001)	-506 [101] (< 0.0001)
ODAHRT	-1220 [41] (< 0.0001)	-1097 [54] (< 0.0001)	-975 [72] (< 0.0001)	-812 [99] (< 0.0001)
ODHRT	-162 [64] (< 0.0001)	-67 [84] (0.4198)	26 [111] (0.8084)	153 [153] (0.3181)
R-squared (adjusted)	0.0798	0.0502	0.0332	0.0234
F(7,13001)	162.24	99.17	64.84	45.55
Prob $> F$	< 0.0001	< 0.0001	< 0.0001	< 0.0001

In general, the results from the net-benefit regression with treatment interaction obtained for the non intent-to-treat cohort were similar to those obtained for the intent-to-

treat cohort for intervention groups ODA and ODAHRT. However, the results for the ODHRT intervention group differed as to which estimates obtained statistical significance. The interaction term formed between the ODHRT intervention group and $\text{age} \geq 65$ was found to be statistically significant at $\lambda = \$0$ and the interaction terms formed with prior fracture were statistically significant at all values of λ . Table 3.59 shows the net-benefit regression estimates with treatment interaction for the non intent-to-treat cohort.

Table 3.59 Non-ITT: Net-benefit regression estimates with treatment interaction

N = 13,008 Explanatory Variables	NMB with $\lambda = \$0$ [se] (p-value)	NMB with $\lambda = \$30,000$ [se] (p-value)	NMB with $\lambda = \$60,000$ [se] (p-value)	NMB with $\lambda = \$100,000$ [se] (p-value)
Constant term	-57 [36] (0.1125)	-219 [47] (< 0.0001)	-382 [62] (< 0.0001)	-598 [86] (< 0.0001)
<i>Covariates</i>				
Age ≥ 65	-402 [62] (< 0.0001)	-573 [81] (< 0.0001)	-744 [108] (< 0.0001)	-972 [149] (< 0.0001)
Steroid > 1-year	-318 [148] (0.0313)	-609 [194] (0.0017)	-901 [258] (0.0005)	-1289 [355] (0.0003)
Statin	46 [34] (0.1729)	136 [44] (0.0022)	226 [59] (0.0001)	346 [81] (< 0.0001)
Prior fracture	-1046 [178] (< 0.0001)	-1839 [234] (< 0.0001)	-2633 [312] (< 0.0001)	-3691 [429] (< 0.0001)
<i>Treatment dummy</i>				
ODA	-843 [57] (< 0.0001)	-772 [75] (< 0.0001)	-701 [99] (< 0.0001)	-606 [137] (< 0.0001)
ODAHRT	-1370 [52] (< 0.0001)	-1305 [69] (< 0.0001)	-1241 [92] (< 0.0001)	-1155 [126] (< 0.0001)
ODHRT	-278 [70] (< 0.0001)	-231 [93] (0.0127)	-183 [123] (0.1369)	-120 [170] (0.4778)
<i>Treatment-covariate interactions</i>				
ODA	188 [86] (0.0285)	185 [113] (0.1010)	182 [150] (0.2261)	178 [207] (0.3900)
Age ≥ 65	307 [87] (0.0004)	419 [114] (0.0002)	531 [152] (0.0005)	681 [209] (0.0011)
ODHRT	377 [189] (0.0464)	451 [249] (0.06980)	525 [331] (0.1132)	623 [456] (0.1716)
Age ≥ 65	200 [195] (0.3062)	407 [256] (0.1125)	614 [341] (0.0722)	890 [470] (0.0581)
Steroid > 1-year	289 [185] (0.1193)	431 [244] (0.0767)	574 [325] (0.0771)	764 [447] (0.0872)
ODHRT	285 [344] (0.4080)	683 [452] (0.1310)	1081 [602] (0.0727)	1612 [829] (0.0518)
ODA	529 [242] (0.0285)	829 [317] (0.0090)	1128 [443] (0.0076)	1528 [581] (0.0086)
Prior fracture	1130 [255] (< 0.0001)	1562 [335] (< 0.0001)	1994 [446] (< 0.0001)	2569 [613] (< 0.0001)
ODHRT	1133 [370] (0.0022)	1756 [486] (0.0003)	2380 [647] (0.0002)	3210 [890] (0.0003)
Prior fracture	0.0821	0.0530	0.0360	0.0260
R-squared (adjusted)	73.72	46.51	31.35	22.67
F(16,12992)	(< 0.0001)	(< 0.0001)	(< 0.0001)	(< 0.0001)
Prob > F				

Post-hoc Analyses

Results from the net-benefit regression with treatment interaction from the primary analyses provided evidence of a statistically significant interaction between the active intervention groups and covariates age ≥ 65 and prior fracture, with both interaction terms suggesting a positive incremental net-benefit. These results beg the question as to whether any of the active treatment interventions are more cost-effective than the comparator intervention group, no treatment. To answer this question, post-hoc net-benefit regression analyses were performed for each of the specific sub-groups.

Presented first are results from the net-benefit regression for the sub-group of patients with a prior fracture for both the intent-to-treat cohort and the non intent-to-treat cohort. The results for the sub-group of patients \geq age 65 are presented next. Since, the primary interest is in the overall cost-effectiveness of the active intervention groups; treatment interaction terms are not included in any of the analyses.

As with the net-benefit regression results for the primary analyses, before the net-benefit regression results for the post-hoc analyses are presented, the estimated mean total cost and mean change in QALYs is provided for each of the intervention groups for both post-hoc analyses for both the intent-to-treat and non intent-to-treat cohorts in Table 3.60.

Table 3.60 Post-hoc analyses: Mean total cost and mean total QALYs by intervention group for the intent-to-treat and non intent-to-treat cohorts

Intervention Group	N	Variable	Mean	Standard Deviation	Minimum	Maximum
Prior Fracture: Intent-to-Treat Cohort						
ODA	157	Total Cost	1,488.88	5,446.30	25.60	67,635.80
		Total QALYS	-0.0253	0.0853	-0.5373	0
ODAHRT	130	Total Cost	1,327.72	858.97	214.82	5,109.29
		Total QALYS	-0.0198	0.0616	-0.3366	0
ODHRT	58	Total Cost	721.58	2,791.50	1.29	21,298.00
		Total QALYS	-0.0236	0.0685	-0.3431	0
ODNOTX	194	Total Cost	909.27	4,152.90	0	39,155.00
		Total QALYS	-0.0397	0.0893	-0.5698	0
Prior Fracture: Non Intent-to-Treat Cohort						
ODA	132	Total Cost	1,517.76	5,854.43	25.60	67,635.80
		Total QALYS	-0.0216	0.0773	-0.5307	0
ODAHRT	105	Total Cost	1,361.03	857.97	214.82	5,109.29
		Total QALYS	-0.0155	0.0549	-0.3366	0
ODHRT	34	Total Cost	240.94	178.79	1.29	740.43
		Total QALYS	-0.0083	0.0419	-0.2437	0
ODNOTX	110	Total Cost	1,313.13	5,209.30	0	39,155.00
		Total QALYS	-0.0347	0.0945	-0.5698	0
Age ≥ 65: Intent-to-Treat Cohort						
ODA	2,549	Total Cost	1,088.72	2,182.70	9.03	67,635.80
		Total QALYS	-0.0088	0.0408	-0.5373	0
ODAHRT	1,775	Total Cost	1,466.19	1,640.66	45.15	34,898.42
		Total QALYS	-0.0056	0.0320	-0.3791	0
ODHRT	222	Total Cost	520.73	2,648.68	.86	22,823.30
		Total QALYS	-0.0078	0.0481	-0.5307	0
ODNOTX	1,894	Total Cost	500.45	3,3638.64	0	82,598.00
		Total QALYS	-0.0124	0.0514	-0.5782	0
Age ≥ 65: Non Intent-to-Treat Cohort						
ODA	2,134	Total Cost	1,116.54	2,299.41	9.03	67,635.80
		Total QALYS	-0.0082	0.0399	-0.5307	0
ODAHRT	1,527	Total Cost	1,504.21	1,516.82	45.15	23,577.27
		Total QALYS	-0.0048	0.0296	-0.3791	0
ODHRT	119	Total Cost	335.64	1,894.81	1.29	20,732.09
		Total QALYS	-0.0058	0.0501	-0.5307	0
ODNOTX	1,263	Total Cost	496.43	3,881.21	0	82,598.00
		Total QALYS	-0.0114	0.0517	-0.5782	0

Patients with a Prior Fracture (Intent-To-Treat)

In general, the results from the net-benefit regression for the patients with a prior fracture sub-group suggests that as the value of λ increases the active interventions become more cost-effective than no treatment. More specifically, the active intervention becomes more cost-effective when $\lambda \geq \$60,000$ for alendronate, $\lambda \geq \$30,000$ for the combination of alendronate and HRT, and $\lambda \geq \$0$ for HRT. However, possibly due to the smaller sample size ($n = 538$) and large standard errors, none of the coefficients for the active interventions at the different values of λ approach the level of statistical significance. Table 3.61 shows the results for the net-benefit regression without treatment interaction for the patients with prior fracture sub-group.

Table 3.61 ITT: Net-benefit regression estimates without treatment interaction for the patients with a prior fracture sub-group

N = 538 Explanatory Variables	NMB with $\lambda = \$0$ [se] (p-value)	NMB with $\lambda = \$30,000$ [se] (p-value)	NMB with $\lambda = \$60,000$ [se] (p-value)	NMB with $\lambda = \$100,000$ [se] (p-value)
Constant term	-820 [331] (0.0136)	-1,964 [436] (< 0.0001)	-3,109 [590] (< 0.0001)	-4,636 [826] (< 0.0001)
<i>Covariates</i>				
Age ≥ 65	-854 [359] (0.0177)	-1,209 [473] (0.0109)	-1,563 [641] (0.0150)	-2,035 [896] (0.0236)
Steroid > 1-year	196 [538] (0.7367)	-852 [768] (0.2674)	-1,901 [1,040] (0.0682)	-3,299 [1,454] (0.0238)
Statin	753 [375] (0.0449)	1,387 [494] (0.0051)	2,019 [669] (0.0026)	2,864 [935] (0.0023)
<i>Treatment dummy</i>				
ODA	-500 [429] (0.2451)	-56 [565] (0.9198)	386 [766] (0.6148)	976 [1,071] (0.3627)
ODAHRT	-456 [450] (0.3113)	127 [592] (0.8300)	710 [802] (0.3765)	1,487 [1,122] (0.1856)
ODHRT	31 [598] (0.9581)	553 [787] (0.4825)	1,074 [1,065] (0.3139)	1,770 [1,491] (0.2357)
R-squared (adjusted)	0.0117	0.0182	0.0238	0.0277
F(6,532)	2.06	2.66	3.19	3.56
Prob > F	0.0559	0.0559	0.0044	0.0018

Patients with a Prior Fracture (Non Intent-To-Treat)

The overall results obtained for the non intent-to-treat cohort were similar to those obtained for the intent-to-treat cohort. However, there were two differences. First, the alendronate treatment became more cost-effective at $\lambda = \$30,000$. Second, the incremental net-benefit at each value of λ for the HRT treatment was considerably higher for the non intent-to-treat cohort compared to the intent-to-treat cohort. Table 3.62 shows the results for the net-benefit regression without treatment interaction for the patients with prior fracture sub-group.

Table 3.62 Non-ITT: Net-benefit regression estimates without treatment interaction for the patients with a prior fracture sub-group

N = 380 Explanatory Variables	NMB with $\lambda = \$0$ [se] (p-value)	NMB with $\lambda = \$30,000$ [se] (p-value)	NMB with $\lambda = \$60,000$ [se] (p-value)	NMB with $\lambda = \$100,000$ [se] (p-value)
Constant term	-1,119 [509] (0.0285)	-1,971 [638] (0.0021)	-2,823 [827] (0.0007)	-3,959 [1,120] (0.0005)
<i>Covariates</i>				
Age ≥ 65	-843 [481] (0.0802)	-1,224 [602] (0.0427)	-1,604 [780] (0.0405)	-2,112 [1,057] (0.0465)
Steroid > 1-year	183 [802] (0.8196)	-920 [1,004] (0.3603)	-2,022 [1,302] (0.1213)	-3,493 [1,764] (0.0485)
Statin	769 [497] (0.1224)	1,136 [622] (0.0685)	1,503 [807] (0.0631)	1,993 [1,093] (0.0690)
<i>Treatment dummy</i>				
ODA	-252 [577] (0.66210)	99 [723] (0.8906)	451 [937] (0.6303)	920 [1,270] (0.4689)
ODAHRT	-218 [613] (0.7221)	275 [767] (0.7197)	769 [994] (0.440)	1,427 [1,348] (0.2904)
ODHRT	696 [893] (0.4360)	1,420 [1,119] (0.2051)	2,143 [1,451] (0.1404)	3,107 [1,965] (0.1147)
R-squared (adjusted)	0.0045	0.0132	0.0193	0.0234
F(6,374)	1.29	1.85	2.25	2.52
Prob > F	0.2657	0.0887	0.0381	0.0213

Patients Age ≥ 65 (Intent-To-Treat Cohort)

Overall, the results from the net-benefit regression for the patients \geq age 65 sub-group provide evidence that treatment with alendronate and the combination of alendronate and HRT are not more cost-effective than no treatment at any value of λ . In contrast, treatment with HRT was found to be more cost-effective than no treatment at values of $\lambda \geq \$30,000$. However, possibly due to large standard errors, none of the coefficients for the ODHRT intervention group approached the level of statistical significance. Table 3.63 shows the results for the net-benefit regression without treatment interaction for the patients ≥ 65 sub-group.

Table 3.63 ITT: Net-benefit regression estimates without treatment interaction for the patients age ≥ 65 sub-group

N = 6,439 Explanatory Variables	NMB with $\lambda = \$0$ [se] (p-value)	NMB with $\lambda = \$30,000$ [se] (p-value)	NMB with $\lambda = \$60,000$ [se] (p-value)	NMB with $\lambda = \$100,000$ [se] (p-value)
Constant term	-515 [66] (< 0.0001)	-919 [85] (< 0.0001)	-1,322 [110] (< 0.0001)	-1,860 [148] (< 0.0001)
<i>Covariates</i>				
Steroid > 1-year	-280 [139] (0.0438)	-436 [179] (0.0151)	-592 [233] (0.0110)	-799 [312] (0.0105)
Statin	141 [66] (0.0335)	308 [86] (0.0003)	476 [111] (< 0.0001)	699 [149] (< 0.0001)
Prior Fracture	-776 [183] (0.0001)	-1,533 [236] (< 0.0001)	-2,289 [307] (< 0.0001)	-3,297 [412] (< 0.0001)
<i>Treatment dummy</i>				
ODA	-594 [79] (< 0.0001)	-493 [102] (< 0.0001)	-392 [132] (0.0030)	-257 [177] (0.1467)
ODAHRT	-960 [86] (< 0.0001)	-754 [110] (< 0.0001)	-547 [144] (0.0001)	-272 [193] (0.1588)
ODHRT	-12 [184] (0.9461)	132 [238] (0.5775)	277 [308] (0.3686)	470 [414] (0.2560)
R-squared (adjusted)	0.0242	0.0170	0.0148	0.0145
F(6,6,433)	27.57	19.59	17.15	16.79
Prob > F	< 0.0001	< 0.0001	< 0.0001	< 0.0001

Patients Age ≥ 65 (Non Intent-To-Treat)

The overall results obtained for the non intent-to-treat cohort were parallel to those obtained for the intent-to-treat cohort for intervention groups ODA and ODAHRT. The only observable difference between the two cohorts for the ODHRT intervention group was that treatment with HRT was more cost-effective than no treatment at all values of λ . Table 3.64 shows the results for the net-benefit regression without treatment interaction for the patients age ≥ 65 sub-group.

Table 3.64 Non-ITT: Net-benefit regression estimates without treatment interaction for the patients age ≥ 65 sub-group

N = 5,042 Explanatory Variables	NMB with $\lambda = \$0$ [se] (p-value)	NMB with $\lambda = \$30,000$ [se] (p-value)	NMB with $\lambda = \$60,000$ [se] (p-value)	NMB with $\lambda = \$100,000$ [se] (p-value)
Constant term	-504 [80] (< 0.0001)	-868 [101] (< 0.0001)	-1,232 [130] (< 0.0001)	-1,716 [174] (< 0.0001)
<i>Covariates</i>				
Steroid > 1-year	-201 [159] (0.2064)	-341 [202] (0.0916)	-481 [260] (0.0640)	-668 [346] (0.0540)
Statin	135 [75] (0.0721)	271 [95] (0.0046)	406 [123] (0.0009)	587 [164] (0.0003)
Prior fracture	-885 [210] (< 0.0001)	-1,529 [267] (< 0.0001)	-2,173 [343] (< 0.0001)	-3,032 [458] (< 0.0001)
<i>Treatment dummy</i>				
ODA	-631 [92] (< 0.0001)	-545 [117] (< 0.0001)	-459 [151] (0.0024)	-344 [202] (0.0887)
ODAHRT	-1013 [99] (< 0.0001)	-817 [126] (< 0.0001)	-621 [162] (0.0001)	-369 [217] (0.0970)
ODHRT	143 [249] (0.56710)	296 [317] (0.3495)	451 [408] (0.2690)	657 [545] (0.2281)
R-squared (adjusted)	0.0254	0.0171	0.0136	0.0134
F(6,5036)	22.86	15.62	12.59	11.37
Prob > F	< 0.0001	< 0.0001	< 0.0001	< 0.0001

Results for Study Hypotheses

In conclusion of the results section, Table 3.65 show the results for study's null hypotheses set forth in Chapter 1.

Table 3.65 Results for the study's null hypotheses

HYPOTHESES	Accept	Reject
OBJECTIVE 2		
H_{O(1)} The odds ratio (OR) of osteoporotic fracture for intervention group ODA = ODHRT = ODAHRT = ODNOTX = 1		X
H_{O(2)} The odds ratio (OR) of osteoporotic hip fracture for intervention group ODA = ODHRT = ODAHRT = ODNOTX = 1		X
H_{O(3)} The odds ratio (OR) of osteoporotic vertebral fracture for intervention group ODA = ODHRT = ODAHRT = ODNOTX = 1		X
H_{O(4)} The odds ratio (OR) of osteoporotic wrist fracture for intervention group ODA = ODHRT = ODAHRT = ODNOTX = 1	X	
OBJECTIVE 4		
H_{O(5)} There is no difference in the proportion of cases free of a osteoporotic fracture event at various points in time between the four intervention groups (ODA, ODHRT, ODAHRT, ODNOTX)		X
H_{O(6)} There is no difference in the proportion of cases free of a osteoporotic hip fracture event at various points in time between the four intervention groups (ODA, ODHRT, ODAHRT, ODNOTX)		X
H_{O(7)} There is no difference in the proportion of cases free of a osteoporotic vertebral fracture event at various points in time between the four intervention groups (ODA, ODHRT, ODAHRT, ODNOTX)		X
H_{O(8)} There is no difference in the proportion of cases free of a osteoporotic wrist fracture event at various points in time between the four intervention groups (ODA, ODHRT, ODAHRT, ODNOTX)		X
H_{O(9)} There is no difference between treatments (ODA, ODHRT, ODAHRT, ODNOTX) in time to osteoporotic fracture after statistically controlling for other covariates (risk factors and statin use)		X
H_{O(10)} There is no difference between treatments (ODA, ODHRT, ODAHRT, ODNOTX) in time to osteoporotic hip fracture after statistically controlling for other covariates (risk factors and statin use)		X
H_{O(11)} There is no difference between treatments (ODA, ODHRT, ODAHRT, ODNOTX) in time to osteoporotic vertebral fracture after statistically controlling for other covariates (risk factors and statin use)		X
H_{O(12)} There is no difference between treatments (ODA, ODHRT, ODAHRT, ODNOTX) in time to osteoporotic wrist fracture after statistically controlling for other covariates (risk factors and statin use)	X	

Chapter 4

Discussion and Conclusions

This chapter discusses the results of objectives one through six, makes concluding remarks, and discusses the study's limitations.

OBJECTIVE 1

The purpose of objective 1 was to assess the epidemiology of osteoporotic fracture in the study population. In the first part, the simple (unadjusted for covariates) three-year cumulative incidence and relative risk of an osteoporotic fracture were determined for the cohort as a whole and by intervention group. In the second part, the simple three-year cumulative incidence and relative risk of an osteoporotic fracture were determined for each risk factor.

Incidence and Relative Risk of Osteoporotic Fracture for the Cohorts and Intervention Groups

During the three-year observation period, a total of 1,238 osteoporotic fractures were reported in the intent-to-treat cohort ($n = 49,851$) and a total of 737 osteoporotic fractures were reported in the non intent-to-treat cohort ($n = 38,283$). The three-year cumulative incidence of osteoporotic fracture ranged from 1.93% for the Non-ITT cohort (5.2% in patients with an osteoporosis diagnosis; 0.24% in patients without an osteoporosis diagnosis) to 2.48% for the ITT cohort (6.1% in patients with an osteoporosis diagnosis; 0.40% in patients without an osteoporosis diagnosis). Table 4.1 provides a comparison of the three-year cumulative incidence and relative risk of fracture for the intent-to-treat and non intent-to-treat cohorts.

Overall the incidence rates and relative risks for osteoporotic fracture were higher in the intent-to-treat compared to the non intent-to-treat cohort. Comparison of the cohort

size and number of fractures between the intent-to-treat and non intent-to-treat cohorts provided an explanation for the difference in osteoporotic fracture incidence rates and relative risks observed between the two cohorts. A total of 11,568 patients in the intent-to-treat cohort deviated from the index-intervention and were subsequently removed, along with their 501 reported fractures. The incidence of osteoporotic fracture in this population was 4.33%, which was over 1.7-fold higher than the incidence experienced in the intent-to-treat cohort. This suggests that patients who experienced an osteoporotic fracture event during the observation period were more likely to have deviated from their index-intervention group.

Unfortunately, a meaningful comparison of the incidence of osteoporotic fracture experienced in the study population to that experienced in the U.S. population is not possible. The National Osteoporosis Foundation (NOF) statistics report the overall total number of osteoporotic fractures and total number by type of osteoporotic fracture without reporting the key piece of information, the size of the population at risk. Instead, to convey the risk of osteoporotic fracture, the NOF typically reports the lifetime risk of the various types of osteoporotic fractures.

Examination of the relative risks of osteoporotic fracture among the active intervention groups compared to the ODNOTX intervention group revealed both expected and unexpected results. As expected, in both the intent-to-treat and non intent-to-treat cohorts the ODAHRT, ODHRT, and NOODTX intervention groups had a lower relative risk of osteoporotic fracture when compared to the ODNOTX intervention group. Unexpectedly, however, the ODA intervention group had the higher relative risk of osteoporotic fracture (except for hip fracture) when compared to the ODNOTX intervention group. This unexpected preliminary result provides the first clue to the possibility of selection bias in the study sample, which will be discussed in greater detail

in objective 2. Among the active intervention groups, the ODHRT intervention group had the lowest relative risk for hip and wrist fracture, whereas the ODAHRT intervention group had the lowest relative risk for vertebral fracture.

Table 4.1 Comparison of three-year cumulative incidence and relative risk of fracture for intent-to-treat and non intent-to-treat cohorts

Intervention Group	Fracture Type	Intent-to-treat		Non intent-to-treat	
		Incidence per 100	Relative Risk	Incidence per 100	Relative Risk
ODA	Hip	1.77	0.91	1.77	0.90
	Vertebral	2.45	1.04	1.87	1.15
	Wrist	2.93	1.27	2.52	1.21
	Total	7.15	1.08	6.16	1.09
ODAHRT	Hip	1.16	0.60	1.19	0.60
	Vertebral	1.46	0.62	0.95	0.58
	Wrist	1.91	0.83	2.00	0.96
	Total	4.53	0.69	4.13	0.73
ODHRT	Hip	0.93	0.48	0.47	0.24
	Vertebral	2.28	0.97	1.42	0.88
	Wrist	1.79	0.78	1.71	0.82
	Total	5.00	0.76	3.61	0.63
ODNOTX	Hip	1.94		1.97	
	Vertebral	2.37		1.62	
	Wrist	2.30		2.09	
	Total	6.61		5.68	
NOODTX	Hip	0.07	0.04	0.05	0.02
	Vertebral	0.30	0.13	0.18	0.11
	Wrist	0.03	0.01	0.01	0.01
	Total	0.40	0.06	0.24	0.04
Cohort	Hip	0.64		0.56	
	Vertebral	0.98		0.62	
	Wrist	0.87		0.74	
	Total	2.48		1.93	

* Reference group: ODNOTX

Cumulative Incidence and Relative Risk of Osteoporotic Fracture by Risk Factor

Literature reports of an increased risk of osteoporotic fracture were substantiated for risk factors: age, osteoporosis diagnosis, previous osteoporotic fracture, and oral

corticosteroid use in both the intent-to-treat and non intent-to-treat cohorts. It is important for the reader to realize, however, that the following reported relative risks associated with the risk factors for objective 1 are not adjusted for the presence of other confounding risk factors. For this reason, a discussion comparing the reported relative risk associated with the various risk factors found in this study to those reported in the literature will be reserved for objective 3.

The relative risk of osteoporotic fracture steadily increased with each successive increase in age-category in both the intent-to-treat and non intent-to-treat cohorts. A diagnosis of osteoporosis was shown to substantially increase the risk of osteoporotic fracture (RR = 15.32 intent-to-treat; RR = 10.55 non intent-to-treat). Similarly, a prior osteoporotic fracture dramatically increased the risk of a subsequent osteoporotic fracture (RR = 11.08 intent-to-treat; RR = 21.92 non intent-to-treat).

The relative risk of osteoporotic fracture associated with oral corticosteroid use and statin use was examined two different ways: the first examined the relative risk regardless of dose and duration of exposure; the second examined the relative risk by dose and duration. Exposure to oral corticosteroids, regardless of dose and duration, increased the risk of osteoporotic fracture by 36% in the intent-to-treat cohort and by 40% in the non intent-to-treat cohort. Examination of corticosteroid dose and duration categories revealed that, in general, the relative risk of osteoporotic fracture substantially increased when the duration of exposure exceeded one-year at all doses. However, evidence supporting a dose-response relationship was inconsistent. Exposure to statins, regardless of dose and duration, decreased the risk of osteoporotic fracture by 34% in the

intent-to-treat cohort and by 29% in the non intent-to-treat cohort. Interestingly statin use was found to have a greater protective effect at low and high doses when the duration of exposure was two-years or less. Intervention compliance, as previously defined, was also shown to have a protective effect for all intervention groups. Table 4.2 shows a comparison of the three-year cumulative incidence and relative risk of fracture for the intent-to-treat and non intent-to-treat cohorts.

Table 4.2 Comparison of three-year cumulative incidence and relative risk of fracture for the intent-to-treat and non intent-to-treat cohorts by risk factor

Risk Factor	Intent-to-treat		Non intent-to-treat	
	Incidence per 100	Relative Risk	Incidence per 100	Relative Risk
Age Category				
50-54	1.03		0.82	
55-59	1.94	1.89	1.41	1.71
60-64	2.53	2.47	1.79	2.18
65-69	2.27	2.21	1.78	2.16
70-74	3.32	3.23	2.70	3.27
75-79	4.04	3.93	3.35	4.07
80-84	5.72	5.57	3.95	4.80
85 Plus	8.39	8.18	6.32	7.68
Osteoporosis Diagnosis				
Exposed	6.10	15.32	18.51	10.55
Non-exposed	0.40		1.75	
Previous Fracture				
Exposed	24.77	11.08	5.20	21.92
Non-exposed	2.24		0.24	
Corticosteroid Use				
Exposed	3.15	1.36	2.50	1.40
Non-exposed	2.32		1.79	
Corticosteroid Use (Dose; Duration)				
< 5mg; ≤ 180 days	1.21	0.52	0.83	0.46
< 5mg; > 180 ≤ 365 days	0.00	0.00	0.00	0.00
< 5mg; > 365 days	8.62	3.72	7.51	4.19
≥ 5 ≤ 10mg; ≤ 180 days	2.62	1.13	2.65	1.48
≥ 5 ≤ 10mg; > 180 ≤ 365 days	1.33	0.57	0.63	0.35
≥ 5 ≤ 10mg; > 365 days	6.60	2.85	4.54	2.53
> 10 ≤ 20mg; ≤ 180 days	2.23	0.96	1.79	1.00
> 10 ≤ 20mg; > 180 ≤ 365 days	4.10	1.77	2.76	1.54
> 10 ≤ 20mg; > 365 days	9.00	3.88	6.57	3.67
> 20mg; ≤ 180 days	2.31	1.00	1.90	1.06
> 20mg; > 180 ≤ 365 days	7.02	3.03	3.80	2.12
> 20mg; > 365 days	4.26	1.83	2.86	1.59

* Reference category for age was the 50-54 age-category

* Reference category for all others was the non-exposed

Table 4.2 Comparison of three-year cumulative incidence and relative risk of fracture for the intent-to-treat and non intent-to-treat cohorts by risk factor (cont'd)

Risk Factor	Incidence per 100	Relative Risk	Incidence per 100	Relative Risk
Statin Use				
Exposed	1.85	0.66	1.52	0.71
Not Exposed	2.80		2.12	
Statin Use (Dose; Duration)				
Low; ≤ 1 year	1.24	0.44	0.99	0.47
Low; $> 1 \leq 2$ years	1.79	0.64	1.35	0.63
Low; > 2 years	2.48	0.88	2.06	0.97
High; ≤ 1 year	1.06	0.38	0.93	0.44
High; $> 1 \leq 2$ years	1.72	0.61	1.30	0.61
High; > 2 years	2.73	0.98	2.44	1.15
Intervention Compliance				
ODA				
Exposed	5.83	0.78	4.90	0.75
Not Exposed	7.51		6.54	
ODHRT				
Exposed	3.16	0.65	3.09	0.70
Not Exposed	4.86		4.40	
ODAHRT				
Exposed	3.85	0.74	3.05	0.82
Not Exposed	5.20		3.71	

* Reference category was the non-exposed

OBJECTIVE 2

The purpose of objective 2 was to determine the effectiveness of the interventions in the prevention of osteoporotic fracture, while controlling for exposure to risk factors and other covariates. A total of eight different logistic regressions were performed for each cohort. The first series (FS) of four logistic regressions were performed to separately determine the intervention effectiveness or fracture risks for each of the intervention groups for any fracture, hip fracture, vertebral fracture, and wrist fracture. This first series of regressions included all five intervention groups, treated the covariate age as multi-categorical, and the covariate oral corticosteroid use as multi-categorical. The second series (SS) of logistic regression differed from the first series in that they: only included the intervention groups with a diagnosis of osteoporosis, treated the covariate age as a continuous variable, and only examined oral corticosteroid use with duration of exposure > 1-year.

Overall, the results from the first series of logistic regression analyses are consistent with the results from the second series of logistic regression analyses. For the intent-to-treat cohort, the ODAHRT intervention group had a statistically significant decreased risk of any fracture (FS: OR = 0.702, 95% CI = 0.579 to 0.851, $p = 0.0003$; SS: OR = 0.698, 95% CI = 0.577 to 0.845, $p = 0.0002$), hip fracture (FS: OR = 0.657, 95% CI = 0.463 to 0.934, $p = 0.0192$; SS: OR = 0.640, 95% CI = 0.453 to 0.906, $p = 0.0117$), and vertebral fracture (FS: OR = 0.576, 95% CI = 0.416 to 0.797, $p = 0.0009$; SS: OR = 0.580, 95% CI = 0.421 to 0.800, $p = 0.0009$). For the non intent-to-treat cohort, the ODAHRT intervention group only showed a decreased risk for vertebral fracture (FS: OR = 0.599, 95% CI = 0.381 to 0.941, $p = 0.0263$; SS: OR = 0.592, 95% CI = 0.378 to 0.928) and the ODHRT intervention group showed a decreased risk of hip fracture (FS: OR = 0.271, 95% CI = 0.085 to 0.869, $p = 0.0281$; SS: OR = 0.282, 95% CI

= 0.088 to 0.905, $p = 0.0333$). Table 4.3 provides a summary of the logistic regression analyses performed to determine intervention effectiveness.

The difference in results obtained for the intent-to-treat and non intent-to-treat cohorts can at least be partially explained by further examination of the population that deviated from their index-intervention. As previously discussed, a total of 11,568 patients deviated from their index-intervention and this population accounted for 501 fractures. Of those 501 fractures, 95 came from the ODA intervention group, 42 from the ODAHRT intervention group, 43 from the ODHRT intervention group, 255 from the ODNOTX intervention group, and 66 from the NOODTX intervention group, representing 29%, 21%, 53%, 51%, and 52% of all reported fractures in the intent-to-treat cohort for each intervention group, respectively. Therefore, the results obtained in the non intent-to-treat cohort are favorably biased for the ODHRT, ODNOTX, and NOODTX intervention groups (over 50% of patients with fractures were eliminated from the analysis). The favorable bias for the ODHRT intervention group helps to explain the statistically significant decreased risk of hip fracture obtained in the non intent-to-treat cohort. The favorable bias for the ODNOTX intervention group indirectly influenced failure of the ODAHRT intervention group not achieving statistical significance for any fracture and hip fracture in the non-intent-to-treat cohort.

With the possible exception of the results obtained for the ODAHRT intervention group, the results obtained in this study do not support the clinical efficacy results reported in clinical trials or the effectiveness results obtained in population based studies. The intervention effectiveness results obtained for alendronate in this study did not approach the level of the statistical significance for a decreased risk of osteoporotic fracture reported in a meta-analysis performed by Kanis et al.¹ In his meta-analysis, alendronate was associated with a statistically significant decreased risk of vertebral

fracture (RR = 0.544, 95% CI = 0.448 to 0.659) and hip fracture (RR = 0.611, 95% CI = 0.392 to 0.951), but was not associated with a statistically significant decreased risk of wrist fracture (RR = 0.866, 95% CI = 0.672 to 1.115). Likewise, the intervention effectiveness results obtained for HRT in this study did not approach those of the Women's Health Initiative (WHI)², which reported that estrogen plus progestin significantly reduced clinical vertebral fractures by 34% and hip fractures by 33% (RH = 0.67; 95% CI = 0.47 to 0.96) and total osteoporotic fractures by 24% (RH = 0.76; 95% CI = 0.69 to 0.83).

As suggested in objective 1, one logical explanation for the failure of the active intervention groups to achieve a statistically significant decreased risk of osteoporotic fracture relative to the ODNOTX group is selection bias. Even though the ODNOTX intervention group had a diagnosis of osteoporosis, this group may have been at a lower risk of fracture compared to the active intervention groups. However, if selection bias is present in the study, then the 29.8% lower odds of any fracture, the 34.3% lower odds of a hip fracture, and the 42.4% lower odds of a vertebral fracture in the ODAHRT intervention group compared to the ODNOTX intervention group are even more impressive.

One possible explanation for the statistically significant decreased risk of any fracture, hip fracture, and vertebral fracture in the ODAHRT group was that the inclusion criteria allowed for previous use of HRT. If the women in the ODAHRT intervention group were initially started on HRT while peri-menopausal or immediately post menopause, they were probably protected from the rapid BMD loss typically experienced at menopause. The validity of this explanation of course hinges on the assumption that members in the other intervention groups were not afforded the same protection of early HRT use.

Table 4.3 Summary of logistic regression analyses for intervention effectiveness

INTENT-TO-TREAT COHORT							
Intervention Group	Fracture Type	1 st Series of Regressions			2 nd Series of Regressions		
		Adjusted Odds Ratio			Adjusted Odds Ratio		
		Point Estimate	95% Confidence Limits		Point Estimate	95% Confidence Limits	
ODA	Any	0.915	0.770	1.087	0.922	0.778	1.093
	Hip	0.763	0.560	1.039	0.750	0.554	1.016
	Vertebral	0.871	0.663	1.143	0.886	0.677	1.159
	Wrist	1.102	0.848	1.431	1.152	0.890	1.490
ODAHRT	Any	0.702	0.579	0.851	0.698	0.577	0.845
	Hip	0.657	0.463	0.934	0.640	0.453	0.906
	Vertebral	0.576	0.416	0.797	0.580	0.421	0.800
	Wrist	0.823	0.616	1.100	0.847	0.552	1.297
ODHRT	Any	0.869	0.659	1.145	0.859	0.652	1.132
	Hip	0.595	0.326	1.087	0.598	0.327	1.091
	Vertebral	1.101	0.739	1.642	1.093	0.733	1.630
	Wrist	0.859	0.560	1.317	0.847	0.552	1.297
NON INTENT-TO-TREAT COHORT							
ODA	Any	0.989	0.798	1.228	0.982	0.794	1.215
	Hip	0.852	0.594	1.221	0.844	0.593	1.202
	Vertebral	1.061	0.730	1.540	1.059	0.733	1.529
	Wrist	1.079	0.777	1.496	1.109	0.803	1.532
ODAHRT	Any	0.806	0.639	1.017	0.795	0.632	1.001
	Hip	0.740	0.494	1.107	0.731	0.491	1.089
	Vertebral	0.599	0.381	0.941	0.592	0.378	0.928
	Wrist	0.961	0.685	1.348	0.980	0.702	1.369
ODHRT	Any	0.834	0.565	1.232	0.835	0.565	1.233
	Hip	0.271	0.085	0.869	0.282	0.088	0.905
	Vertebral	1.275	0.706	2.302	1.270	0.703	2.296
	Wrist	0.920	0.527	1.608	0.904	0.518	1.579

*Bolded = $p < 0.05$

OBJECTIVE 3

The purpose of objective 3 was to determine the significance of the risk factors and other covariates in the prediction of osteoporotic fracture, while controlling for exposure to other risk factors and covariates. Two different logistic regressions were performed for each cohort. The first series (FS) of logistic regressions performed included all five intervention groups, treated the covariate age as categorical, and the covariate oral corticosteroid use as multi-categorical. The second series (SS) of logistic regression differed from the first series in that they: only included the intervention groups with a diagnosis of osteoporosis, treated the covariate age as a continuous variable, and only examined oral corticosteroid use with duration of exposure > 1-year. Both the first series and the second series of logistic regressions examined the significance of the risk factors and other covariates for any fracture.

The results from the first series of logistic regression analyses suggested that age could be better treated as a continuous variable and that the focus of the risk associated with oral corticosteroid use should be limited to oral corticosteroid use with duration of > 1-year. Moreover, since the focus of this study is on the effectiveness of the active interventions, a decision was made to only include the intervention groups with a diagnosis of osteoporosis in the second series of logistic regression analyses. Since the overall results from the first series and second series of logistic regression analyses for the intent-to-treat and non intent-to-treat cohorts are consistent, the following discussion focuses on the results obtained in the second series of logistic regression analyses. For the sake of completeness, a summary table of risk factor and other covariate significance for the first series of regression results are presented in Table 4.4.

Risk factors age, prior fracture, and corticosteroid use were shown to significantly increase the risk of osteoporotic fracture. Age was shown to be a strong predictor of osteoporotic fracture, with nearly identical results obtained for the intent-to-treat and non intent-to-treat cohorts (ITT: OR = 1.047, 95% CI = 1.039 to 1.055; Non-ITT: OR = 1.047, 95% CI = 1.037 to 1.056). The strongest predictor of an osteoporotic fracture was prior fracture (ITT: OR = 4.279, 95% CI = 3.401 to 5.382; Non-ITT: OR = 3.446, 95% CI = 2.548 to 4.66). Oral corticosteroid use duration > 1-year was also shown to significantly increase the risk of osteoporotic fracture (ITT: OR = 1.553, 95% CI = 1.220 to 1.977; Non-ITT: OR = 1.379, 95% CI = 1.037 to 1.056).

Intervention compliance in the ODAHRT intervention group and statin use were shown to decrease the risk of osteoporotic fracture. Intervention compliance in the ODAHRT intervention group was shown to have a weak protective effect only in the intent-to-treat cohort (OR = 0.610, 95% CI = 0.390 to 0.953). However, this protective effect is probably more a function of the overall treatment effectiveness exhibited in the ODAHRT intervention group. Statin use was found to have a protective effect for statin categories: low dose \leq 1-year (ITT: OR = 0.417, 95% CI = 0.307 to 0.566; Non-ITT: OR = 0.410, 95% CI = 0.276 to 0.609), low dose > 1-year \leq 2-years (ITT: OR = 0.616, 95% CI = 0.454 to 0.834; Non-ITT: OR = .627, 95% CI = 0.427 to 0.921), low dose > 2-years (ITT: OR = 0.648, 95% CI = 0.518 to 0.811; Non-ITT: OR = 0.649, 95% CI = 0.492 to 0.857), and high dose < 1-year (ITT: OR = 0.472, 95% CI = 0.269 to 0.827; Non-ITT: OR = 0.490, 95% CI = 0.240 to 1.000), but was not found to have a statistically

significant protective effect in the high dose $> 1\text{-year} \leq 2\text{-years}$ or the high dose $> 2\text{-years}$ category.

The risk factors shown to be associated with a statistically significant risk of osteoporotic fracture in this study coincide with those reported in the literature. This study provides evidence that the odds of women having an osteoporotic fracture increased over 4% for each year over the age of 50. Although not directly comparable, these results show the same trend as the National Osteoporosis Foundation's predicted 5-year probabilities of various types of fractures at various ages for average-risk Caucasian women (Table 1.2). This study found an approximate 4-fold increase in the odds of having an osteoporotic fracture in patients with a prior fracture. The literature similarly reports that a past history of postmenopausal fracture confers a 4-fold increase in the risk of hip fracture relative to a negative fracture history³ and that vertebral fracture increases the risk of additional fractures by at least 4-fold (independent of BMD).⁴ The literature reports that corticosteroid therapy is the most common cause of drug-related osteoporosis, with an estimated 30-50% of patients receiving chronic corticosteroid therapy experiencing fractures.⁵ In this study, only 309 of the 9,797 (3.15%) oral corticosteroid users experienced a fracture during the 3-year observation period, however the odds of experiencing an osteoporotic fracture was 35 to 55% higher among chronic oral corticosteroid users whose exposure exceeded a 1-year duration.

Perhaps the most surprising result for objective 3 was the protective effect of statins on osteoporotic fracture. Although the aim of this study was not to perform an epidemiological study to examine a causal relationship between statin exposure and

osteoporotic fracture, to my knowledge this was the first study to examine exposure of statins by dose and duration. The results from this study suggest that statins may have a protective effect for osteoporotic fracture regardless of dose or duration. Although the high dose $> 1\text{-year} \leq 2\text{-years}$ and high dose $> 2\text{-years}$ category did not achieve statistical significance, examination of the confidence intervals for both dose and duration categories at least suggest a trend towards a protective effect. Table 4.5 provides a summary of the second series of logistic regression analyses for risk factors and other covariates of significance

Table 4.4 Summary of the first series of logistic regression analyses for risk factors and other covariates of significance

Risk Factor	Intent-to-Treat			Non Intent-to-Treat		
	Adjusted Odds Ratio			Adjusted Odds Ratio		
	Point Estimate	95% Wald Confidence Limits		Point Estimate	95% Wald Confidence Limits	
Age Category						
55 - 59	1.412	1.082	1.843	1.280	0.909	1.804
60 – 64	1.601	1.252	2.048	1.460	1.064	2.002
65 – 69	1.898	1.435	2.512	1.650	1.158	2.352
70 – 74	2.713	2.042	3.604	2.347	1.642	3.356
75 – 79	3.108	2.349	4.112	2.863	2.021	4.055
80 – 84	4.730	3.456	6.474	3.727	2.493	5.573
≥ 85	6.194	4.307	8.910	5.665	3.633	8.832
Corticosteroid Use						
<5mg; ≤180 days	0.505	0.223	1.144	0.428	0.135	1.351
<5mg; >180≤365 days	< 0.0001	< 0.0001	> 999.99	<0.001	<0.001	>999.999
<5mg; >365 days	1.674	1.119	2.503	1.733	1.036	2.899
≥5≤10mg; ≤180 days	0.984	0.702	1.380	1.221	0.827	1.802
≥5≤10mg; >180≤ 365 days	0.479	0.151	1.517	0.271	0.037	1.961
≥5≤10mg; >365 days	1.387	0.977	1.967	1.083	0.663	1.768
>10≤ 20mg; ≤180 days	0.906	0.655	1.254	0.924	0.611	1.397
>10≤ 20mg; >180≤365 days	1.404	0.673	2.930	1.107	0.399	3.076
>10≤ 20mg; >365 days	2.153	1.359	3.413	2.096	1.163	3.776
>20mg; ≤180 days	0.964	0.757	1.228	0.925	0.678	1.263
>20mg; >180≤365 days	2.249	0.949	5.328	1.295	0.305	5.499
>20mg; >365 days	1.705	0.399	7.293	1.233	0.162	9.389

*Boded = p < 0.05

Table 4.4 Summary the first series of logistic regression analyses for risk factors and other covariates significance (cont'd)

Risk Factors	Intent-to-Treat			Non Intent-to-Treat		
	Adjusted Odds Ratio			Adjusted Odds Ratio		
	Point Estimate	95% Wald Confidence Limits		Point Estimate	95% Wald Confidence Limits	
Intervention Compliance						
ODA 80% MPR	0.739	0.537	1.017	0.741	0.514	1.069
ODHRT 80% MPR	0.768	0.360	1.637	0.670	0.232	1.938
ODAHRT 80% MPR	0.616	0.394	0.963	0.663	0.413	1.063
Statin Use						
Low; ≤1 year	0.417	0.313	0.556	0.414	0.284	0.603
Low; >1≤ 2 years	0.626	0.471	0.834	0.601	0.412	0.877
Low; >2 years	0.653	0.526	0.811	0.666	0.508	0.872
High; ≤1 year	0.418	0.239	0.731	0.445	0.219	0.907
High; >1≤ 2 years	0.639	0.390	1.047	0.654	0.333	1.286
High; >2 years	0.747	0.526	1.060	0.757	0.488	1.176
Previous Fracture						
Previous Fracture	4.229	3.358	5.326	3.422	2.527	4.634

*Bolded = p < 0.05

Table 4.5 Summary the second series of logistic regression analyses for risk factors and other covariates significance

Risk Factor	Intent-to-Treat			Non Intent-to-Treat		
	Adjusted Odds Ratio			Adjusted Odds Ratio		
	Point Estimate	95% Wald Confidence Limits		Point Estimate	95% Wald Confidence Limits	
Age						
Age	1.047	1.039	1.055	1.047	1.037	1.056
Intervention Compliance						
ODA 80% MPR	0.743	0.540	1.022	0.744	0.516	1.071
ODHRT 80% MPR	0.779	0.366	1.659	0.691	0.239	1.996
ODAHRT 80% MPR	0.610	0.390	0.953	0.659	0.411	1.057
Corticosteroid Use						
≤ 1-year	0.907	0.758	1.084	0.895	0.715	1.121
≥ 1-year	1.553	1.220	1.977	1.379	1.002	1.898
Statin Use						
Low; ≤1 year	0.417	0.307	0.566	0.410	0.276	0.609
Low; >1≤ 2 years	0.616	0.454	0.834	0.627	0.427	0.921
Low; >2 years	0.648	0.518	0.811	0.649	0.492	0.857
High; ≤1 year	0.472	0.269	0.827	0.490	0.240	1.000
High; >1≤ 2 years	0.626	0.369	1.060	0.554	0.258	1.189
High; >2 years	0.686	0.471	1.001	0.756	0.482	1.187
Previous Fracture						
Previous Fracture	4.279	3.401	5.382	3.446	2.548	4.660

*Bolded = p < 0.05

OBJECTIVE 4

There were two general goals for objective 4: 1) to describe the proportion of cases free of a fracture event at various points in time, and 2) to assess the relationship between survival time and a set of covariates to determine whether treatment differences exist after statistically controlling for the other covariates.

Kaplan-Meier Life Tables and Survival Plots

The Kaplan-Meier method of life tables was used to describe the proportion of cases free of a fracture event at various points in time. Life tables and survival plots were constructed to describe the proportion of cases free of any fracture event, hip fracture event, vertebral fracture event, and wrist fracture event at various points in time

Results for the intent-to-treat cohort and non intent-to-treat cohorts revealed that there were statistically significant differences in survival functions between the intervention groups for: any fracture event, hip fracture event, vertebral fracture event, and wrist fracture event ($p < 0.0001$). As expected, examination of the Kaplan-Meier estimates (survival) revealed that the NOODTX intervention group had the greatest probability that a patient would be fracture-free at each duration interval for any fracture and for each specific type of fracture. In the intent-to-treat cohort, among intervention groups with an existing osteoporosis diagnosis, the ODAHRT intervention group had the greatest probability that a patient would be fracture-free at each duration interval for any fracture and for vertebral fracture. For hip fracture, the ODAHRT intervention group had the greatest probability that a patient would be fracture-free for up to 1 ½ years. At 1 ½

years or more, the ODHRT intervention group had the highest probability that a patient would be fracture-free. Similarly for wrist fracture, the ODAHRT intervention group had the greatest probability that a patient would be fracture-free up to two years. At two years or more, the ODHRT intervention group had the highest probability that a patient would be fracture-free. The Kaplan-Meier life tables and survival plots for the non intent-to-treat cohort mirrored those of the intent-to-treat cohort, with one notable exception in which the ODHRT intervention group had the greatest probability that a patient would be fracture-free for any fracture after approximately 2 ½ years. The explanation for the difference in results obtained for the intent-to-treat and non intent-to-treat cohorts are the same as described for objective 2.

The Kaplan-Meier life tables and survival curves provide an unadjusted estimate of intervention effectiveness. From these results, it appears that treatment with the combination of alendronate and HRT provide the highest probability of survival for any fracture and vertebral fracture and the highest probability of survival for hip and wrist fracture for the first half of the observation period, at which point treatment with HRT alone provides the highest probability of survival. However, these results do not account the presence of confounding covariates.

Cox Proportional-Hazards Model

A direct Cox proportional-hazards model was used to assess the relationship between survival time and the set of covariates. The primary purpose of this analysis was to determine if there was a difference in survival time between intervention groups after adjusting for the effects of the other covariates. A total of eight different logistic

regressions were performed for each cohort. The first series (FS) of four separate logistic regressions were performed to determine the hazard ratio for each of the intervention groups for any fracture, hip fracture, vertebral fracture, and wrist fracture. This first series of regressions included all five intervention groups, treated the covariate age as multi-categorical, and the covariate oral corticosteroid use as multi-categorical. The second series (SS) of logistic regression differed from the first series in that they: only included the intervention groups with a diagnosis of osteoporosis, treated the covariate age as a continuous variable, and only examined oral corticosteroid use with duration of exposure > 1-year.

Overall, the results from the first series of logistic regression analyses are consistent with the results from the second series of logistic regression analyses. For the intent-to-treat cohort, the ODAHRT intervention group had a statistically significant decreased risk of any fracture (FS: HR = 0.711, 95% CI = 0.590 to 0.856; SS: HR = 0.708, 95% CI = 0.589 to 0.851), hip fracture (FS: OR = 0.673, 95% CI = 0.476 to 0.950; SS: HR = 0.658, 95% CI = 0.467 to 0.925), and vertebral fracture (FS: HR = 0.578, 95% CI = 0.420 to 0.796; SS: HR = 0.584, 95% CI = 0.425 to 0.801). For the non intent-to-treat cohort, the ODAHRT intervention group only showed a decreased risk for vertebral fracture (FS: HR = 0.601, 95% CI = 0.384 to 0.940; SS: HR = 0.593, 95% CI = 0.380 to 0.926) and for hip fracture (HR = 0.799, 95% CI = 0.640 to 0.999) in the second series of logistic regressions only. The ODHRT intervention group showed a decreased risk of hip fracture (FS: HR = 0.278, 95% CI = 0.087 to 0.866); SS: HR = 0.288, 95% CI = 0.090 to 0.918). Table 4.6 provides a summary of the logistic regression analyses performed to determine intervention effectiveness.

The results obtained for the logistic regression analyses are remarkably similar to those obtained in the Cox proportional-hazards regression, not only in the overall results

but also in the size of the coefficients. This normally would suggest that time is not a significant factor in determining the effectiveness of the interventions. However, the Cox proportional-hazards model used in this study violated the assumption of proportional hazards, which means one or more of the covariates interacted with time. The consequence of violating the proportional hazards assumption is that the coefficient, for the variable which varied with time, represents more of an average effect for the variable over time, thus information is lost and results may be misleading.⁶ Although not presented in the results section, an attempt was made to analyze the data set using a non-proportional hazards model. Two covariates were identified as having a significant interaction with time, the intervention groups and age. Unfortunately, the non-proportional hazards model failed to provide an interpretable interaction effect for both age and the intervention group covariates, especially the ODHRT intervention group.

The significance of the risk factors and other covariates in the direct Cox proportional hazards model were nearly identical to those obtained in the logistic regression analyses. For this reason, a separate discussion of their significance is not provided.

The results obtained from the direct Cox proportional-hazards model are disappointing in that they afforded no additional information than what was gained from the logistic regression analyses. However, evidence of an interaction between the intervention groups and time does suggest that further research is warranted.

Table 4.6 Summary results of Cox regression analyses for intervention effectiveness

INTENT-TO-TREAT COHORT							
Intervention Group	Fracture Type	1 st Series of Regressions			2 nd Series of Regressions		
		Relative Hazard			Relative Hazard		
		Hazard Ratio	95% Confidence Limits		Hazard Ratio	95% Confidence Limits	
ODA	Any	0.914	0.775	1.077	0.925	0.787	1.088
	Hip	0.789	0.584	1.065	0.785	0.584	1.054
	Vertebral	0.863	0.661	1.126	0.881	0.677	1.147
	Wrist	1.102	0.852	1.426	1.151	0.893	1.484
ODAHRT	Any	0.711	0.590	0.856	0.708	0.589	0.851
	Hip	0.673	0.476	0.950	0.658	0.467	0.925
	Vertebral	0.578	0.420	0.796	0.584	0.425	0.801
	Wrist	0.824	0.619	1.098	0.845	0.636	1.122
ODHRT	Any	0.867	0.664	1.130	0.857	0.657	1.118
	Hip	0.613	0.338	1.109	0.613	0.339	1.111
	Vertebral	1.088	0.735	1.609	1.077	0.728	1.594
	Wrist	0.858	0.563	1.309	0.847	0.555	1.292
NON INTENT-TO-TREAT COHORT							
ODA	Any	0.987	0.803	1.215	0.985	0.803	1.208
	Hip	0.877	0.618	1.246	0.880	0.624	1.243
	Vertebral	1.049	0.726	1.515	1.050	0.730	1.509
	Wrist	1.082	0.783	1.494	1.112	0.808	1.529
ODAHRT	Any	0.810	0.646	1.014	0.799	0.640	0.999
	Hip	0.750	0.504	1.115	0.746	0.504	1.105
	Vertebral	0.601	0.384	0.940	0.593	0.380	0.926
	Wrist	0.961	0.688	1.343	0.980	0.704	1.363
ODHRT	Any	0.834	0.571	1.220	0.834	0.570	1.219
	Hip	0.278	0.087	0.886	0.288	0.090	0.918
	Vertebral	1.264	0.705	2.267	1.258	0.701	2.259
	Wrist	0.920	0.529	1.598	0.904	0.521	1.570

OBJECTIVES 5 & 6

In objective 5, the incremental cost-effectiveness of the treatment interventions was determined while statistically controlling for the presence of risk factors and other covariates by employing the net-benefit regression method of cost-effectiveness analysis. The same methodology was employed in objective 6, where the importance of covariates on the marginal cost-effectiveness of an intervention was determined by examining interaction effects between each intervention and important patient subgroups.

As in the previous analyses, two separate analyses were performed, one for the intent-to-treat cohort and the other for the non intent-to-treat cohort. For each cohort, two separate analyses were initially performed, one without treatment interaction and the other with treatment interaction. Results from the primary analyses provided evidence of a statistically significant positive incremental net-benefit for interaction terms formed between the active intervention groups and covariates age ≥ 65 and prior fracture. Therefore, subsequent post-hoc analyses were performed to determine if any of the active interventions were cost-effective in these sub-groups.

Results from Primary Analyses

Results from the net-benefit regression without treatment interaction showed that the incremental net-benefits for all active treatment interventions were less than the incremental net-benefit for no treatment in both the intent-to-treat and non intent-to-treat cohorts. The incremental net-benefit for treatment with alendronate and the combination of alendronate and HRT were statistically significantly less than no treatment for all values of λ . In contrast, the incremental net-benefit for treatment with HRT, although lower, was not statistically significantly lower than no treatment at λ values $\geq \$30,000$.

In the second analysis with treatment interaction, interaction terms were formed between each active intervention group and covariates: age ≥ 65 , oral corticosteroid use > 1 -year, and prior fracture. The results from the net-benefit regression with treatment interaction revealed that all of the treatment interactions achieved a positive incremental net-benefit. For treatment with alendronate, the net-benefit regression with treatment interaction results showed a statistically significant positive incremental net-benefit with age ≥ 65 for values of $\lambda \leq 30,000$ and prior fracture for values of $\lambda \geq \$30,000$. Similarly, treatment with the combination of alendronate and HRT achieved a statistically significant positive incremental net-benefit with age ≥ 65 and prior fracture for all values of λ . Likewise, patients in the ODAHRT intervention group with a prior fracture achieved higher net-benefits from treatment in comparison to patients without a prior fracture for all values of λ . In the intent-to-treat cohort, the only significant interaction term formed between treatment with HRT and a covariate was with prior fracture and this interaction term only became statistically significant at $\lambda \geq \$60,000$. In the non intent-to-treat cohort, the interaction term formed between treatment with HRT and age ≥ 65 was found to be statistically significant at $\lambda = \$0$ and the interaction terms formed with prior fracture were statistically significant at all values of λ . Although higher net-benefits were observed for the interaction terms formed between intervention groups and the covariate corticosteroid use > 1 -year, none of these were found to be statistically significant.

Post-hoc Analyses

In general, the results from the net-benefit regression for the sub-group of patients with a prior fracture sub-group suggests that as the value of λ increases, the active interventions become more cost-effective than no treatment. More specifically, the active intervention becomes more cost-effective when $\lambda \geq \$30,000$ (non intent-to-treat cohort) or $\$60,000$ (intent-to-treat cohort) for the alendronate, when $\lambda \geq \$30,000$ for the

combination of alendronate and HRT, and when $\lambda \geq \$0$ for HRT. However, none of the coefficients for the active interventions at the different values of λ approach the level of statistical significance.

Overall, the results from the net-benefit regression for the sub-group of patients \geq age 65 provide evidence that treatment with alendronate and the combination of alendronate and HRT are not more cost-effective than no treatment at any value of λ . In contrast, treatment with HRT was found to be more cost-effective than no treatment at all values of λ (non intent-to-treat cohort) or at values of $\lambda \geq \$30,000$ (intent-to-treat cohort). However, none of the coefficients for the ODHRT intervention group approached the level of statistical significance.

Summary of Results

Results from the net-benefit regression without treatment interaction suggest that there is not a statistically significant difference in the cost-effectiveness between treatment with HRT and no treatment at values of $\lambda \geq \$30,000$, which is the threshold of cost-effectiveness established by the NOF. Results from the net-benefit regression with treatment interaction and post-hoc analyses provide evidence of a trend in which treatment with HRT in the high-risk subgroups (age ≥ 65 and prior fracture) becomes more cost-effective than no treatment.

Results from the net-benefit regression without treatment interaction reveal that treatment with alendronate and the combination of alendronate and HRT were statistically significantly less cost-effective than no treatment for all values of λ . However, the results from the net-benefit regression with treatment interaction and post-

hoc analyses suggest a trend in which treatment with alendronate or the combination of alendronate and HRT become more cost-effective than no treatment for patients with a prior fracture when $\lambda \leq \$30,000$ for alendronate and when $\lambda \geq \$30,000$ for the combination of alendronate and HRT.

The results from this study suggest that current treatment interventions employed by the DoD are not cost-effective in the prevention of osteoporotic fractures. These results, to some extent, contradict the cost-effectiveness studies found in the literature for the various interventions. There are four primary reasons or explanations as to why the current treatment interventions were not found to be cost-effective: 1) the interventions were expensive, 2) the value for the effect variable (quality-adjusted life-years (QALYs)) was small, 3) only direct medical costs were included in the model, and 4) the risk of fracture in the population was possibly low.

As with other published studies, the intervention costs were the primary driver of costs in this study. The intervention costs used in this study reflected either the acquisition cost to the DoD or the “total submitted amount due” to the managed care contractor. Unlike previous HRT cost-effectiveness studies which only used the average cost for oral HRT dosage forms, this study used the actual cost for each HRT oral dosage form and used the actual cost of the more expensive transdermal preparations. Therefore, the costs for HRT intervention and the combination of alendronate and HRT may have been somewhat higher in this study compared to those of previously published studies.

In this study, the effect on QALYs was probably lower than those reported in previous studies for primarily three reasons. First, this study only examined the change

in QALYs over the three-year observation period, whereas other studies that predominantly employed long-term cost-effectiveness models examined the effect on QALYs over the life of the patient. Second, this study employed age-adjusted empirically derived health state values (HSVs), which were substantially higher (less of a decrement to QALYs) than expert-opinion derived HSVs used in previously published studies. Lastly other studies, particularly those involving HRT, included the non-skeletal impact on QALYs such as relief from menopausal symptoms and decreased risk of cardiovascular disease.

Many of the previously published long-term cost-effectiveness studies included direct non-medical costs, indirect costs, and mortality costs in addition to direct medical costs to justify the cost-effectiveness for a particular intervention. In contrast, this study only included the direct medical cost associated with an osteoporotic fracture. Failure to account for the costs associated with discharge to an orthopedic rehabilitation facility or long-term care in a nursing home resulting from a hip fracture and mortality associated with a hip fracture is a considerable limitation of this study.

This study reflects the actual use of osteoporotic fracture interventions in the DoD population. The population used was arguably at a lower risk of fracture than the populations used to determine the clinical efficacy of a treatment intervention in randomized controlled trials or the hypothetical population used in many of the long-term cost-effectiveness models. As demonstrated in this study, selected use of an osteoporotic fracture intervention in a higher risk population provided more favorable cost-effectiveness outcomes.

CONCLUSION

The epidemiologic study results showed that in the study population of females age ≥ 50 DoD beneficiaries, an osteoporotic fracture was a relatively rare event, with a three-year cumulative incidence of an osteoporotic fracture ranging between 1.93 to 2.48 % for the population. The intent-to-treat analysis revealed that the three-year cumulative incidence of osteoporotic fracture in patients with an osteoporosis diagnosis (6.1%) was 15-fold higher than in those without an osteoporosis diagnosis (0.4%).

If the possible presence of selection bias is ignored, the intervention effectiveness results from both the logistic regression model and the direct Cox proportional-hazards model suggest that women treated with the combination of alendronate and HRT are at a lower risk for any fracture, hip fracture, and vertebral fracture when compared to no treatment, while statistically controlling for the presence of risk factors and other covariates. In contrast, treatment with alendronate or HRT alone was not found to provide a statistically significant decreased risk of any fracture, hip fracture, vertebral fracture, or wrist fracture when compared to no treatment, while statistically controlling for the presence of risk factors and other covariates. The effectiveness results for alendronate and HRT in the prevention of osteoporotic fracture from this study contradict the efficacy results obtained in the clinical trials for alendronate and the effectiveness results obtained for HRT in the WHI. For this reason, the presence of selection bias cannot be ignored and it's suggested that additional statistical measures need to be performed to diagnose the level of selection bias and attempt to correct for its presence.

The results of this study support published reports of a statistically significant relationship between age, corticosteroid use, and prior osteoporotic fracture and an increased risk of osteoporotic fracture. This study provides evidence that the risk of osteoporotic fracture increases: 4-fold with a prior fracture, 4% with each year over 50,

and between 38 and 55% with oral corticosteroid use > 1-year (in a three-year period). This study also provides evidence of not only a statistically significant relationship between statin use and a decreased risk of osteoporotic fracture, but also that such effect is independent of dose and duration.

The primary focus of this research was the application of the net-benefit regression method of CEA to determine the cost-effectiveness of the DoD's current anti-osteoporotic fracture interventions. The results from this study suggest that globally current use of the treatment interventions is not cost-effective in the short-term when compared to no treatment. However, this study also provides evidence that the current treatment interventions become more cost-effective when targeted at high risk populations, such as patients with a prior osteoporotic fracture. Here again, these results are potentially influenced by the presence of selection bias and also warrant that additional statistical measures be performed to diagnose the level of selection bias and if at all possible correct for its presence.

LIMITATIONS

When interpreting the results of this study, it is important to consider the potential limitations which might affect the internal and construct validity of the study results. As previously discussed, the primary limitation and threat to the internal validity of this study was the possible presence of selection bias. In general, selection bias may be present if knowledge of the disease affects selection or classification of exposed (active intervention group) and non-exposed (control group) individuals to be included in the study. In this study, the concern is whether patients who received an active intervention (exposed) were at a greater risk of osteoporotic fracture compared to those in the control group (non-exposed). More specifically, patients in the ODNOTX intervention group may have had a lower risk of osteoporotic fracture compared to those patients in the active intervention groups (ODA, ODAHRT, and ODHRT), thus biasing the results to the null hypothesis. The results obtained in this study suggest that the intervention groups were not at equal risk, especially the ODA intervention group, and that selection bias may be present.

Perhaps the second biggest limitation of this study and threat to internal validity is confounding by other risk factors not included in the model, which in this case is somewhat related to the potential presence of selection bias. This study included all risk factors and potentially important covariates that were obtainable from the health care claims and prescription databases. However, at least two important risk factors (BMD and race) were not available and were not included in the analyses, and thus may potentially confound the results.

This study was limited in that it only examined of the short-term (three-year) cost-effectiveness of the DoD's current osteoporosis interventions, thus ignoring long-term costs and consequences associated with osteoporotic fracture. Moreover, this study only

examined the direct medical costs associated with the prevention and treatment of osteoporotic fracture that were readily available from the health care and prescription claims databases. Significant costs associated with discharge to rehabilitation centers and nursing homes was not included nor did this study account for mortality and its associated costs.

Another potential limitation and threat to the internal validity of this study was the use of administrative health care and prescription claims data for an unintended use. In this study, health care claims data provided the diagnostic information used to determine fracture events. These data were potentially subject to under- and over-coding and data entry errors for a variety of reasons to include, reimbursement systems, provider behavior, and/or documentation systems. Furthermore, prescription claims data only indicates that a prescription was dispensed, thus requiring the assumption that the patient actually took the medication as prescribed using the proper technique, which is a big assumption with alendronate.

A threat to construct validity and another potential limitation of this study were the operational definitions employed to diagnose a new osteoporotic fracture. Initially, the intent was to adopt the same operational definitions employed by Westfall et al. However, since approximately 8% of the health care claims did not contain a primary procedure code, a more conservative operational definition of a new osteoporotic fracture event was employed. This more conservative definition was not jointly exhaustive and mutually exclusive and could have potentially resulted in an under-representation of the actual number of fracture events.

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Vita

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